Increasing Diversity in Clinical Trials: Best Practices

Health Disparities Symposium

October 2, 2003

Office of Special Populations and Research Training
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

EXECUTIVE SUMMARY

The Office of Special Populations and Research Training (OSPRT) of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), hosted the health disparities symposium titled Increasing Diversity in Clinical Trials: Best Practices, at the Bethesda Marriott Hotel in Bethesda, Maryland, on Thursday, October 2, 2003. The symposium attracted approximately 150 attendees, representing a broad spectrum of disciplines in clinical trials research and practice.

The purpose of the symposium was to bring together clinical researchers, community physicians, nurse coordinators, community advisory board members, and other health care professionals with an interest in increasing the racial and ethnic diversity of participants in clinical trials. The symposium explored culturally appropriate methodologies in the outreach, recruitment, and retention of racial and ethnic minority participants in clinical trials.

The symposium objectives were to

- Examine cultural issues that affect the recruitment and retention of minority participants in clinical trials
- Provide researchers, outreach workers, and community educators with effective strategies for outreach, recruiting, and retaining participants from minority populations
- Demonstrate best practices for utilizing electronic resources to identify applicable policies governing clinical trials and human subjects and for identifying funding sources and mechanisms

Symposium events included a plenary session, panel discussion, three concurrent breakout sessions, three presentations, and concurrent session reports.

The symposium commenced with opening remarks by Dr. Milton Hernandez, Director of OSPRT, and a welcome statement by Dr. Anthony S. Fauci, Director of NIAID. The keynote speaker for the symposium was Dr. Neil Powe, a professor at the Johns Hopkins Medical Institutions and director of the Welch Center for Prevention, Epidemiology, and Clinical Research in Baltimore, Maryland. Dr. Milton Hernandez provided closing remarks.

Results from the overall evaluation forms and the anecdotal comments indicate that NIAID clearly reached its objectives for the symposium and that the symposium was well received by the attending professionals. Nearly all the participants (92 percent) either agreed or strongly agreed that the symposium increased their knowledge and understanding of culturally appropriate methodologies in the outreach, recruitment, and retention of racial and ethnic minority participants in clinical trials.

Two survey instruments were developed to collect data about the symposium and the concurrent breakout sessions. For the overall symposium, the instrument consisted of 10

close-ended and 4 open-ended questions. The survey for the concurrent breakout sessions consisted of five close-ended questions and two open-ended questions. Both surveys provided space for additional comments. Question 4 of the concurrent session instrument, although close ended, also allowed space for comments. Statistics used in the symposium are descriptive, and anecdotal comments extracted from the surveys are listed in their respective sections. See the Appendices section of this report for copies of the evaluation instruments.

A panel discussion following the opening remarks consisted of a moderator and four presenters:

- Moderator: Jane Delgado, Ph.D., M.S., President and Chief Executive Officer, National Alliance for Hispanic Health, Washington, D.C.
- Victoria A. Cargill, M.D., MSCE, Director of Minority Research and Director of Clinical Studies, Office of AIDS Research, NIH, Bethesda, Maryland
- Jacquelyn Fleckenstein, M.D., Associate Professor of Medicine, University of Tennessee, Memphis, Tennessee
- Donna Mildvan, M.D., Chief, Division of Infectious Diseases, and Principal Investigator, AIDS Clinical Trials Unit, Beth Israel Medical Center, New York, New York
- Herman E. Mitchell, Ph.D., Senior Research Scientist, Rho Federal Systems Division, Inc., Chapel Hill, North Carolina

Three concurrent breakout sessions were held at the end of the morning session, as follows:

Session 1: After the Clinical Trial—Then What?

Moderator: Paula Strickland, Ph.D., Acting Director, Office of International Extramural Activities, Division of Extramural Activities, NIAID, NIH, Bethesda, Maryland

Discussion Leaders:

- Marian C. Limacher, M.D., Professor of Medicine, University of Florida College of Medicine, Gainesville, Florida
- Deneen Robinson, B.S.W., HIV Treatment Consultant, Dallas, Texas

Session 2: Minority Investigators in Clinical Trials—How Important Are They?

Moderator: Jenise Gillespie, Ph.D., R.N., Nurse Consultant, Office of the Director, Division of Microbiology and Infectious Diseases, NIAID, NIH, Bethesda, Maryland

Discussion Leaders:

- Clemente Diaz, M.D., Professor and Chairman, Department of Pediatrics, University of Puerto Rico, San Juan, Puerto Rico

- Michele K. Evans, M.D., Deputy Scientific Director, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland

Session 3: Role of the Community Advisory Board and Outreach Activities

Moderators:

- Diane Adger-Johnson, Minority Health and Research Training Analyst, OSPRT, Division of Extramural Activities, NIAID, NIH, Bethesda, Maryland
- Joyce Hunter Woodford, M.P.P., Minority Health and Training Program Officer, OSPRT, Division of Extramural Activities, NIAID, NIH, Bethesda, Maryland

Discussion Leaders:

- Anne Madey, B.S., R.N., Research Nurse Coordinator, University of Tennessee Health Science Center, Memphis, Tennessee
- Matthew Murguia, Director, Office of Program Operations and Scientific Information, Division of AIDS, NIAID, NIH, Bethesda, Maryland

Three individual presentations were delivered during the afternoon session, as follows:

Clinical Trials Resources

- Wilma Templin-Branner, M.S., Medical Education and Outreach Group, Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee

Why Primary Care Physicians Don't Refer Their Patients

- John Hogan, M.D., Medical Officer, Unity Health Care, Inc., Washington, D.C.

Recruitment and Retention: What Works and Why?

- Kathleen B. Drennan, Chief, Global Marketing and Strategic Business Development, Iris Global Clinical Trials Solutions, Chicago, Illinois
- Donald P. Orr, M.D., Professor of Pediatrics, Nursing Research, and Dietetics and Nutrition, and Director of Adolescent Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Following the individual presentations, the discussion leaders summarized the breakout session discussions.

Symposium Surveys

A survey was administered at the close of each breakout session and at the conclusion of the symposium for the purpose of evaluating the following:

- Overall effectiveness of the initial clinical trials symposium
- Effectiveness of the individual breakout sessions
- Effectiveness of the speakers and of the information and materials disseminated during the symposium and concurrent sessions
- Gathering suggestions and comments about what is desired and needed to diversify clinical trial participation
- Obtaining information that would be useful and/or would enhance future clinical trial symposia

Additional Information

For more information on the symposium outcomes, please contact

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HEALTH DISPARITIES SYMPOSIUM

Thursday, October 2, 2003

OPENING REMARKS

Milton Hernandez, Ph.D., Director, Office of Special Populations and Research Training, Bethesda, Maryland

Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland

Dr. Milton Hernandez welcomed participants to the health disparities symposium, "Increasing Diversity in Clinical Trials: Best Practices," sponsored by the Office of Special Populations and Research Training (OSPRT) of the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH). He remarked that in planning the symposium, OSPRT hoped to select the best topics and speakers and draw on the experience and expertise of the audience regarding best practices to increase diversity in clinical trials.

Dr. Hernandez introduced Anthony S. Fauci, M.D., who has been the Director of NIAID since 1984. As Director, Dr. Fauci oversees an extensive portfolio of basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including HIV/AIDS and other sexually transmitted diseases, tuberculosis, malaria, autoimmune disorders, asthma, allergies, and illnesses from potential agents of bioterrorism.

Dr. Fauci welcomed the participants to the symposium. He mentioned NIAID's efforts to increase its diversity in the clinical trials process. As the second largest of the 27 National Institutes of Health, NIAID is particularly intent on having diversity in its clinical trials on infectious and immune-mediated diseases. Dr. Fauci pointed out that the same segments of society that bear a disproportionate burden of diseases also face unfair disparities in access to quality health care. One of the mechanisms of good access to health care is diversity in clinical trials. NIAID's 2001 Strategic Plan for Addressing Health Disparities was subsumed into the broad NIH Strategic Plan, and NIAID has been the lead Institute in addressing health disparities.

Dr. Fauci explained that the health disparities symposium would address some of the critical cultural issues involved in the recruitment and retention of minorities in clinical trials as well as the role of minority investigators, community advisory boards, and primary care physicians in the clinical trial process.

CULTURAL ISSUES IN THE RETENTION OF MINORITY POPULATIONS IN CLINICAL TRIALS

Neil Powe, M.D., M.P.H., M.B.A., Professor, Johns Hopkins Medical Institutions; Director, Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, Maryland

Dr. Powe's presentation addressed cultural issues in the recruitment and retention of minorities in clinical trials. In a two-pronged approach to the subject, Dr. Powe (1) examined the demographic information related to NIH extramural clinical trial recruitment, disease burden, and mortality rates in minority populations and (2) laid out a conceptual framework regarding issues that hinder minority participation.

Demographic Information

Data from the *NIH Blue Report*, published in December 2002, reveal information about minority participation in NIH extramural clinical trials by racial and ethnic group. Data from fiscal year 2000 can be used to compare the percentage of the population in different minority groups with the percentage of the minority groups in NIH studies. The data show that 12.1 percent of the U.S. population is African American, and 11.3 percent of subjects in NIH clinical studies are African American. The data also reveal that 12.5 percent of the U.S. population is Hispanic, but only 7.9 percent of subjects in NIH studies are Hispanic. However, NIAID did significantly better in the recruitment of both groups: 28 percent of patients in NIAID studies are African American and 11.2 percent are Hispanic.

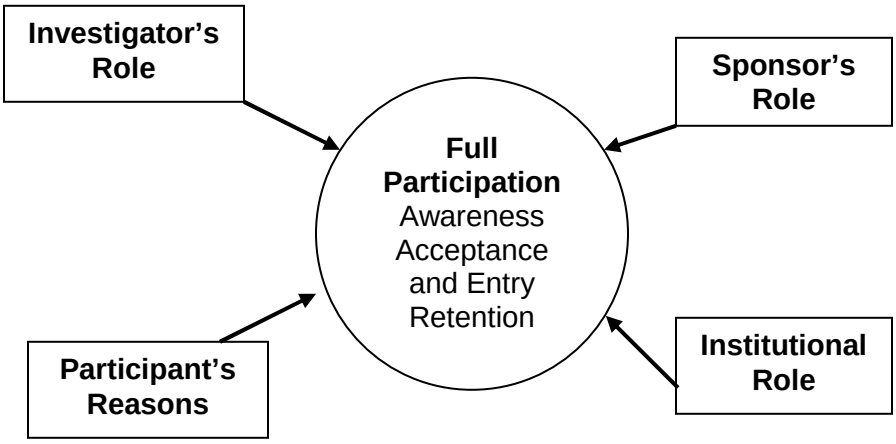
The question involves the appropriate target number. The census reflects the overall proportion of patients in the population, but the burden of disease varies by race and ethnicity. The burden of disease can be described by many measures, including incidence, prevalence, total mortality, years of life lost, hospital days, and disability adjusted life years. Regarding HIV burden, 50 percent of AIDS cases are African American, 19 percent of cases occur in Hispanics, 64 percent of female HIV cases are African American, and 54 percent of new HIV infections occur among African Americans. Those statistics reveal that NIAID is falling below the appropriate target number for enrollment of participants in clinical trials. An examination of prevalence of disease by race and ethnicity also reveals a disproportionate burden of asthma among African Americans, of diabetes among Hispanics and African Americans, and of alcohol consumption among whites and Hispanics. Regarding death rates by race and ethnicity, heart disease, lung cancer, and breast cancer kill a disproportionate number of African Americans. Dr. Powe called for an examination of conditions and use of a variety of measures of burden of disease to arrive at appropriate targets for minority enrollment in clinical trials. The statistics suggest that NIH's efforts in minority enrollment may not be as successful if examined from the point of view of appropriate targets.

Conceptual Framework and Barriers to Minority Participation

Dr. Powe offered a conceptual framework to achieve the full participation of minorities in clinical trials. The framework includes the participant's reasons for joining a study, the

investigator's role, the sponsor's role, and the institutional role, as depicted in the figure below.

Framework To Achieve Full Participation in Clinical Trials



Dr. Powe described the three steps that participants must take to enroll in clinical studies and gave examples of various factors that might influence each of the steps:

1. *The patient must be aware of the study.* However, studies have shown that race, ethnicity, and socioeconomic status can affect a person's awareness of studies. A household telephone survey in Baltimore[1] to determine the health information sources used by women (print health media, regular news media, broadcast media, computer resources, health organizations, and organized health events) found that whites are much more likely than African Americans to use print news media (64 percent versus 44 percent), computer resources (45 percent versus 21 percent), and health organizations (21 percent versus 7 percent). Dr. Powe pointed out that use of information sources affects utilization of health care.

2. *The patient must be aware of the terms of the study and be willing to enter it.* Acceptance is based on perceived harm and perceived benefit, which often depend on health status. Patients with poor health status will try many interventions and will enroll in a trial if it means the possibility of a cure. Other patients may not be so inclined. Past experiences with the health care system also can affect acceptance or willingness to enter a study. In addition, trust in the investigator or sponsor, altruism, and religiosity can affect acceptance. In a recent study, Dr. Giselle Corbie-Smith[2] at the University of North Carolina designed a national cross-sectional telephone survey, randomly sampled 527 African Americans and 382 whites from the general

[1] Nicholson WK, Grason HA, Powe NR. The relationship of race to women's use of health information resources. Am J Obstet Gynecol 2003;188:580-5.
[2] Corbie-Smith G, Thomas SB, St George DM. Distrust, race, and research. Arch Intern Med 2002;162:2458-63.

population, and administered the 45-minute survey. On a seven-item scale of distrust developed by Dr. Corbie-Smith, the survey found the following results:

- 15 percent of African Americans versus 8 percent of whites do not believe they could freely ask their physicians questions.
- 37 percent of African Americans versus 20 percent of whites believe their physician would ask them to participate in medical research even if he or she thought it would harm them.
- 47 percent of African Americans versus 23 percent of whites do not trust their physician to fully explain research participation.
- 45 percent of African Americans versus 34 percent of whites believe that physicians sometimes expose patients to unnecessary risk.
- 79 percent of African Americans versus 51 percent of whites believe that it is very likely or somewhat likely that people might be used as guinea pigs.
- 62 percent of African Americans versus 8 percent of whites believe physicians very often or fairly often prescribe medication as a way of experimenting.
- 24 percent of African Americans versus 8 percent of whites believe that physicians have given them treatment as part of an experiment without their permission.

In general, the study found that African Americans have higher distrust scores than whites (mean score of 3.1 among African Americans and 1.8 among whites). Distrust was associated with lower education, unemployment, male sex, and geographic region. After adjustment for sociodemographic factors that differ between the races, African Americans still had almost 5 times the odds versus whites of having a distrust score of 5 or greater. Dr. Powe commented on this national study's profound results.

Another cross-sectional study of willingness to participate in a hypothetical heart disease prevention trial[3] used a random/consecutive sample of outpatients treated at 13 Maryland internal medicine and cardiology clinics during 2002. The patients were adults who presented for a medical visit, who spoke English or used an interpreter, and who were able to comprehend the nature of a 15-minute, self-administered questionnaire. The questionnaire included a description of the research study and its objectives, risks and benefits to the patient, the voluntary nature of the study, requirements to be met by the patients during the length of the study, alternative treatment options, the right to withdraw, the study sponsor, the presence of potential investigator conflicts, and the rewards for joining. Respondents were asked about their willingness to join the study. When Dr. Corbie-Smith's medical research distrust index was used, it was found that those respondents with a higher level of distrust were less likely to join the trial than those who had none or a low level of distrust; therefore, distrust is associated with willingness to join. More African Americans were unlikely or very unlikely to join the hypothetical trial than whites. African Americans were much more likely to have higher distrust scores than whites. Thus,

[3] Braunstein JB, Schulman SP, Powe NR. Effect of Ethnicity on Distrust Toward Medical Researchers and Willingness to Join Clinical Trials. J Am Coll Cardiol 2003; 41:534A.

addressing the issue of distrust might address why African Americans are unlikely to join trials.

Another study addressed African Americans and participation in AIDS research.[4] This cross-sectional study of 301 African Americans in Durham, North Carolina, found through in-person interviews that 50 percent of the African Americans would not participate in AIDS-related clinical trials. Distrust was the strongest inverse predictor of willingness to participate, along with a variety of other factors that were also associated with willingness to participate. Dr. Powe pointed out that these findings indicate that distrust is a very important issue that must be addressed.

3. *The patient must be retained in the study over the life of the study.* A framework to achieve full participation in clinical trials addresses participant barriers, investigator barriers, sponsor barriers, and institutional barriers:

    - *Participant barriers* to full participation in clinical trials include knowledge and education (limited opportunities to learn about research, concerns about changing medical regimens, fatalistic attitudes about chances for recovery), sociocultural factors (beliefs and moral values, religion, language, mistrust, negative experience with hospital or injury due to treatment, family and friends' influence, beliefs about alternative medicine), and economic factors (caring for children or other ill relatives that might prevent participation in trials, working multiple jobs, transportation, lack of medical resources in the community).

    - *Investigator barriers* to full participation in clinical trials include issues of study design and implementation (ineffective guidance to study staff, recruitment based on convenience, study run-in periods and selection processes, ineffective informed consent processes), communication (limited knowledge about methods to increase awareness, ineffective study staff communication, stereotypes and attitudes of investigators, lack of feedback), and resources (lack of community liaison efforts, limited knowledge of appropriate retention methods).

    - *Institutional and sponsor barriers* to full participation in clinical trials include the lack of investigator incentives, rewards, and penalties for not enrolling in a clinical trial; lack of funds to address difficult recruitment and participant incentives; and institutional stereotypes and attitudes that must be dismissed to achieve full participation.

Dr. Powe described some of the promising practices or interventions to address the barriers. In terms of *awareness,* promising practices might be a physician taking time to explain and complete the study paperwork, adding additional staff or monetary incentives, providing free or reduced care, doctors encouraging other doctors to involve their patient populations in clinical trials, and effective communication or advertisement from community leaders, local newspapers, and churches. In terms of *illiteracy and*

[4] Sengupta S et al. Factors affecting African-American participation in AIDS research. J Acquir Immune Defic Syndr 2000;24:275-84.

language barriers, interventions might include using translators and alternatives to written communication, providing taxi vouchers or vans to address transportation issues, using community members as research staff, using peer groups and community-based participatory research methods, using outreach efforts to emphasize the value of participation, providing child and elder care, and creating simplified informed consent forms. In terms of *retention,* promising practices include allowing more flexibility in scheduling examinations and followup, making the clinical environment more friendly, involving minority research staff, involving physicians in the study, creating newsletters that track the progress of the study, and acknowledging patients through cards and gifts.

Dr. Powe stated that some issues in enrollment can be addressed through community-based participatory research strategies, such as involving members of the target population in the planning efforts of the trial, taking the message to the target population, using a community spokesperson to empower patients to join research, and giving back to the community through jobs, gifts, screenings, and clinical tests.

Dr. Powe called attention to the existence of fear and mistrust. He pointed out that the recruitment strategies used in the Tuskegee study (1932–1972) included a community-based approach with local black churches, the Macon County Medical Society, local plantation owners, local public schools, the Tuskegee Institute, black physicians, and boards of health. The Tuskegee study offered free physicals, food, transportation, and burial stipends to gain permission for autopsies from family members. Similar strategies are being advocated for HIV education and AIDS risk reduction programs today, but the value of these community-based strategies is not diminished by their association with the Tuskegee study. The issues of mistrust must be addressed.

Ethical considerations in recruitment involve patients' understanding of the consent form, doctor referrals, use of incentives, and minority-only studies, which heighten fear and mistrust in some minority populations because of suspicion of a study targeting only one minority population. However, minority-only studies result in clear evidence of efficacy for specific minority populations and justice in monetary distribution of research funds.

Dr. Powe ended his presentation by stating that recruiting minorities remains a challenge even though NIH policies on tracking recruitment have led to more attention and progress in this arena. A variety of barriers exist to awareness, recruitment, and retention of minorities in clinical trials. Distrust is a significant barrier among the African American population, and language is a significant barrier among the Hispanic population. However, promising strategies are emerging to overcome barriers in a way that will maintain ethical standards.

Discussion

Dr. Powe's presentation raised the following issues and questions:

- An epidemiologist raised the question of the distinction between mistrust and stigma. Mistrust comes from actual events that occurred in past research trials and

experiments involving African Americans. Participants were correct to mistrust a health care system that operated without honesty or integrity. However, the institutional review board (IRB) process and community advisory boards have now succeeded in removing the stigma associated with clinical trials.

- Another participant commented on the provider barrier and the disrespectful treatment of community providers by institutions that perform clinical trials. Dr. Powe responded that one way to address this problem is with focus groups of community physicians who plan the objectives of a study and give input about recruitment and enrollment. NIH's idea of reengineering the clinical enterprise, referred to by Dr. Fauci, involves establishing a national core of community physicians who would be involved in research and empowered to be part of studies.

- Another participant asked Dr. Powe to elaborate on the institutional barriers, in particular, regarding stereotypes and attitudes. Dr. Powe explained that there are very few studies that track provider attitudes and stereotypical views. One study of providers' attitudes toward minority patients of low socioeconomic status showed that providers assumed that minorities would not comply with research protocols. Their "fatalistic attitude" has a negative impact on their inclination to enroll minorities in research studies.

- Another participant mentioned barriers in terms of funding, in particular, regarding outreach and the use of plain language in informed consent documents. Dr. Powe remarked that these issues can be dealt with through more involvement with institutional leadership roles (e.g., on IRB committees) to call attention to the difficulties and ways to address them. The direct involvement and experience of individuals in positions of leadership can influence the issues that are addressed.

PANEL DISCUSSION

The Nuts and Bolts of Successful Recruitment and Retention: Success Stories/Work in Progress

Dr. Hernandez introduced the panel discussion on successful recruitment and retention, which included success stories and work in progress. Dr. Jane Delgado, who moderated the panel of distinguished scientists, is the president and chief executive officer of the National Alliance for Hispanic Health, the Nation's largest and oldest organization of providers serving Hispanics. The National Alliance for Hispanic Health was previously called COSSMHO (National Coalition of Hispanic Health and Human Services Organizations); it serves more than 12 million Latinos annually. Dr. Delgado is a practicing clinical psychologist and the author of many books, including *Salud: A Latina's Guide to Total Health,* the first health book written by and for Latinos.

Jane Delgado, Ph.D., M.S., President and Chief Executive Officer, National Alliance for Hispanic Health, Washington, DC

Dr. Delgado affirmed the commitment of the National Alliance for Hispanic Health to clinical trials and facilitating the participation of Hispanics in clinical trials. She described a recent incident in which one of her friends was admitted to an intensive care unit at a local hospital. Shortly after being treated for a heart attack, he was asked to sign a consent form for participation in a clinical trial and he was subjected to an uncomfortable echocardiogram. Dr. Delgado noted that the content of the consent form was acceptable but that the context in which it was used was questionable. She stated that her friend's informed consent experience made her question the informed consent process, specifically, when and how the process is begun.

Victoria A. Cargill, M.D., MSCE, Director of Minority Research, and Director of Clinical Studies, Office of AIDS Research, NIH

Dr. Victoria A. Cargill stated that, regarding clinical trials, stereotyping and decisions are based more on the power of distribution in our society than on scientific reasons for excluding certain key populations. She explained that clinical trials can fail to meet the needs of marginalized populations. A proof of concept might be interesting to a researcher, but it is not interesting to a woman with a viral infection and two sick babies who has to take four buses to get to a study location. In addition, clinical trials sometimes do not address issues of importance to the community. They end up being done *to* the community instead of *with* the community; they can be characterized as "drive-by" research.

Given these circumstances, how can recruitment and retention be successful? Dr. Cargill remarked that successful recruitment and retention will occur within the community when researchers "think outside the box," expand their horizons, and allow the community to be their teachers. She stated that researchers must be user friendly for the potential participant, not for themselves. She reported on a clinical trial targeted to women with HIV infection. By definition, most of the eligible women were women of color, many of them single mothers with limited income. The recruitment for the study was slow at first. Not surprisingly, the study was conducted in a place with fixed hours, no transportation provided, and no "perks." Dr. Cargill pointed out that the study should have expanded its hours to include nights and weekends and should have addressed challenges such as providing onsite childcare. To operationalize a study, the study planners must respect the barriers. For example, taxicab vouchers can offset transportation barriers. In addition, Dr. Cargill suggested providing something in return to the participants—either additional education, clinical trial buddies, or town hall meetings to share the study results with the community.

Dr. Cargill commented on the need to reduce structural barriers, including institutional racist barriers. Stereotyping must be eliminated, and the needs and challenges of the target population must be learned. A balance also must be struck between coercion and respecting time commitments. In addition, one strategy cannot work for all participants. Recruitment must be targeted to individuals.

As Dr. Cargill explained, thinking outside the box means acting outside the box, including taking the following steps:

- *Addressing individual barriers* involves identifying issues, reducing or modifying them when possible, and including staff members who reflect the patient population at all levels. Dr. Cargill pointed out that the target population often has no one to speak for them in an authentic way and that they are beset with genuine fear, mistrust, and a disinclination to speak up on their own behalf. She affirmed that community-based organizations and what they can provide are often overlooked.

- *Reducing structural barriers* involves taking action on providing childcare, transportation, and study buddies.

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- *Creating unique collaborations and partnerships* might involve a technical specialist who provides a voice mailbox to participants and links it to a call-in computer that acts as an advice-giver.

- *Realizing that special populations are not aliens* means recognizing individuals' core desires and needs.

Dr. Cargill concluded by citing a Chinese proverb: "Study without reflection is a waste of time; reflection without study is dangerous." She referred to a pharmacokinetics study involving pregnant women. The study involved several blood draws done in a hospital over a protracted period of time. Dr. Cargill credited NIAID with providing transportation, childcare, and a person to explain the various aspects of the study to the participants. As a result, the women had the opportunity to learn about HIV and pregnancy. Many of the women have remained much more engaged in their care than they were before. This win-win situation can be replicated elsewhere.

Jaquelyn Fleckenstein, M.D., Associate Professor of Medicine, University of Tennessee, Memphis, Tennessee

Dr. Jaquelyn Fleckenstein stated that she is participating in a NIAID U-19 Cooperative Hepatitis C Research Center project titled "Racial Differences in HCV/Host Interactions." The principal investigator (PI) is Dr. Caroline Reilly, Dr. Fleckenstein is the project leader, and Ms. Anne Madey is the study coordinator. The substudy is titled "The African American Response to Therapy for Hepatitis C." Dr. Fleckenstein remarked on the unusual circumstance of having two minorities run this project and mentioned that Dr. Reilly is one of the few female PIs in the Hepatitis C Cooperative Centers.

One of the major health issues today, hepatitis C infects about 3.8 million Americans. The prevalence in African American men between the ages of 40 and 49 is 10 percent. In 1997, Dr. Fleckenstein and her colleagues carried out a multicenter study looking at treatment for hepatitis C with interferon and ribavirin, which at the time was the best therapy available. They enrolled a total of 341 patients, including 34 African Americans, which is very small amount, particularly because of the high prevalence of hepatitis C in

the African American population. Dr. Fleckenstein noted striking differences in response rates between Caucasians and African Americans. Caucasians had a 49-percent overall response rate, whereas African Americans had a 4.8-percent response rate. This difference sparked the researchers' interest, and they submitted an application for funding to study the phenomenon.

The current study entails treatment with pegylated interferon and ribavirin, which is now the standard treatment. The enrollment goal for this small, single-center study is 75 African Americans and 50 Caucasians. The enrollment process will probably take 2 months, followed by 48 weeks of labor-intensive treatment and 6 months of followup. The therapy involves a multitude of side effects. The data on response rate indicate that the African American subjects probably have a 20-percent chance of a cure and the Caucasians have a 50- to 60-percent chance of a cure. Enrollment for this 4-year study began in 2001. Thus far, 78 patients have been enrolled—46 African Americans and 32 Caucasians. Of the 46 African Americans, 31 are female and 15 are male. Dr. Fleckenstein remarked that African American men are the least likely to participate in clinical trials because they have the greatest sense of mistrust. On the other hand, of the 32 enrolled Caucasians, 18 are males and 14 are females.

The researchers' initial efforts were focused on recruitment. Retention has not been a problem because of the study design. The clinical research center provides easy access, parking, and scheduling. The participants see the same study coordinator each visit, the same physician is always available, and the physicians often help participants with their other medical problems. The clinical research center includes a large proportion of minority providers; in fact, a popular African American phlebotomist helped retention dramatically. In addition, the study coordinator is very helpful to the researchers, and the clinical research center helps provide food stamps and transportation.

Recruitment efforts for the study included physician referral letters, advertisements in resident clinics, and volunteering in local clinics such as the Church Health Clinic, which provides care to the working class who have no insurance. In return for being able to see the patients with hepatitis C, the researchers also agreed to provide liver care for anyone, on request. Dr. Fleckenstein stated that she also recruited at the VA hospital, where the prevalence of hepatitis C is 10 percent for all patients. The researchers also participated in health fairs and screenings, increased their participation in a local hepatitis support group, and created a branch of the American Liver Foundation in Memphis. In addition, they established outreach programs in community health clinics.

In assessing all these strategies, Dr. Fleckenstein noted that the physician referral letters were completely ineffective. Also, the clinic advertisements were not at all beneficial. In addition, although the health fairs and screenings have not provided any additional patients, they have increased awareness in the community and provided access to testing for patients. The biggest disappointment was in the VA recruitment. Dr. Fleckenstein also noted the complete lack of success in obtaining IRB approval for the study, not because of risks related to the treatment, but because of the use of genetic testing and banking specimens.

The successful strategies related to the "African American Response to Therapy for Hepatitis C" study included volunteering at the Church Health Clinic, which began in 2001. Referrals from the clinic's minority providers began to be very frequent beginning in the past year. The researchers' continued input and their willingness to treat all patients made their participation in the clinic a successful recruitment strategy. Another successful strategy involved using nursing support staff at resident clinics and community health clinics. Nurse practitioners helped outreach efforts. Providing open access for patients and direct contact with doctors' offices was another strategy. If a patient was referred, he or she would be seen immediately. Likewise, direct contact between a minority nurse practitioner and minority physicians' offices resulted in referrals. The hepatitis support groups, after a period of many months with regular participation, also proved fruitful for recruitment. The 50-percent African American population of Memphis was another key factor in the successful recruitment for the study.

Donna Mildvan, M.D., Chief, Division of Infectious Diseases, and Principal Investigator, AIDS Clinical Trials Unit, Beth Israel Medical Center, New York, New York

Dr. Donna Mildvan presented information about a work in progress—the Adult AIDS Clinical Trials Group (AACTG), the largest HIV clinical trials organization in the world, which has played a major role in setting the standard of care for HIV treatment. In collaboration with academia throughout the world and with industry, AACTG has been responsible for designing and conducting trials that have led to the licensing of the now 19 available agents for the treatment of HIV disease as well as anti-opportunistic infection and malignancy therapies. Moreover, AACTG is composed of leading clinical scientists in HIV/AIDS therapeutic research.

The focuses of AACTG are (1) pathogenesis-based therapeutic interventions, (2) treatment strategies to limit replication of HIV-1 and improve disease-free survival among infected individuals, (3) rapid development of agents that prevent or delay the complications of HIV-related disorders, (4) HIV-1 pathogenesis through advanced laboratory investigation, (5) recruitment and retention of clinical trial participants who reflect the changing demographics of the AIDS epidemic, and (6) therapeutic approaches that improve quality of life for persons with HIV-1 infection. Beginning with its inception in the late 1980s, AACTG has been committed to recruiting participants from at-risk populations for the clinical trials process. AACTG has had impressive successes in the treatment of HIV disease commensurate with its understanding of these populations. With AACTG's understanding that single agent treatment was going to fail and that therapy had to be directed toward multiple targets in the HIV life cycle, and with the introduction of protease inhibitors, dramatic declines in mortality began to occur.

The declines in mortality, however, have not necessarily been reflected to the same degree across all the populations affected by HIV. CDC data through the year 2001 show no leveling off of the AIDS incidence curve among black and Hispanic individuals in this country. The devastation of AIDS continues in U.S. cities. In the 2001 data, of the 816,000 AIDS cases reported to the CDC, blacks and Hispanics accounted for 57 percent

of the total cases, for 78 percent of all women who had been reported to CDC, for 79 percent of all heterosexuals, and for 82 percent of all children diagnosed with AIDS by 2001. Confronted with these statistics, some like-minded individuals proposed the formation of a small working group within AACTG to focus on the changing face of the epidemic. AACTG endorsed the formation of the Underserved Populations Working Group, whose goal was to develop proposals designed to increase minority representation in clinical trials. The question asked was "Were there issues around the design of clinical trials themselves that would enable an increase in the diversity of their patient populations?"

Dr. Mildvan and her colleagues wanted to increase the critical mass of individuals who were committed to this goal by inviting PIs, senior investigators, and past and present Minority AIDS Training Program (MATP) fellows to join the working group. Dr. Mildvan and her colleagues also invited individuals from the community constituency group and the patient care committee. This year, the working group conducted the first review for selection of the 2003 MATP fellow, who has joined the working group. Dr. Mildvan presented the list of members. The cochair, Kimberly Smith, is a graduate of the MATP fellowship program. Another member, Toyin M. Adeyemi, is also a graduate of the MATP fellowship program and is very committed to the goal of the working group. Other fellows include William King from UCLA, Donna DeFreitas from California, and the newest member, Obiamiwe Umeh. The diversity within the working group illustrates the group's universal commitment to the common goal.

The Underserved Populations Working Group had its first conference call around the same time that an article by Gifford and colleagues in the *New England Journal of Medicine*[5] pointed out the important discrepancy between nationwide AIDS demographic information and participation in NIH clinical trials. The working group took that information very personally because figure 2 in the article was a bar graph referring to AACTG clinical trials. The group also thought that the timing was perfect because it raised the awareness of disparity in the AIDS clinical trials program and increased interest in its goal.

The white, not Hispanic proportion of the AIDS population represents a minority of AIDS cases in the United States but a majority of participants in clinical trials and an impressive majority of individuals to whom experimental medication has been given. Dr. Mildvan stated that the presented data reflect a period of time between 1996 and 1998; she and her colleagues wanted to ask the question, "What do our data look like now within the AACTG?" She pointed out that they collected very good data from all 35 AIDS Clinical Trials Units (ACTUs) around the country, and each ACTU has its own very well-documented accrual rates for the four populations of interest. In addition, once a year, each of the sites must present its regional demographics to NIH; therefore, the ratio between the particular site and the regional demographics could be calculated to determine which sites are overperforming compared with their expected regional demographics.

[5] Gifford AL et al. Participation in research and access to experimental treatments by HIV-infected patients. N Engl J Med 2002;346(18):1400-2.

The target is a ratio of accrual to regional demographics greater than or equal to 1.0. Such a ratio would indicate a site that was successful in recruiting a particular patient population. For the 2001–2002 evaluation year, 41 percent of the participating sites around the country met or exceeded the target for women. For blacks, only 17 percent of the ACTUs met or exceeded the target. For Hispanics, 44 percent met the target, and for injecting drug users, only 19 percent met the target. For the entire AACTG accrual over the national statistics, the ideal would be a ratio of 1.0; that ratio was not approximated for many of the populations of interest.

For the current evaluation year, 2002–2003, the data show improvement in every category in the proportion of sites that achieved or exceeded the accrual compared with the regional demographics. Dr. Mildvan explained that her group also wanted to identify other possible successful strategies that the overperforming sites might have developed. In addition, they wanted to ascertain whether the year that a particular study was conducted and the type of study question contributed to successes in accrual of minority populations.

Dr. Mildvan described an ongoing study that will yield very important information. The same Dr. Gifford who published the *New England Journal of Medicine* article that was the wakeup call for many is now conducting a comparative study across two protocols to examine recruitment and retention in trials as a function of baseline factors in patients: reasons for trial enrollment, attitudes and beliefs about retention, depressive symptoms and perceived stress, social demographics and social support systems, and alcohol and substance use. In addition, descriptive site surveys were conducted within AACTG to share best-practice information. A document was distributed in 1997 and updated in 2002 by the Patient Care Committee. The Underserved Populations Working Group wants to take the next step in data gathering. It created the Questionnaire Focus Group led by the MATP investigators, who are developing a questionnaire to link the site performance data to site investigator attitudes and beliefs regarding recruitment and retention. It is expected that the statistical analysis resulting from the survey will be very informative.

Dr. Mildvan described two exploratory proposals that are works in progress. These proposals are looking for models for potential export from successful sites to the entire group and for development of clinical trial curricula that are culturally sensitive and specific. Dr. Mildvan explained that she envisions developing partnerships with AIDS service organizations and working with community-based organizations. In addition, the benefit or effect of a clinical trial could be shown. This phenomenon has been well described in the cancer literature; that is, participants in clinical trials—even in the conventional arm—do better than individuals who do not participate in clinical trials. The same could be the case in HIV disease. Finally, can trials be designed that answer questions relevant to the targeted population? For example, anemia and HIV-associated nephropathy occur at much higher rates in African Americans than in whites. A case-controlled study is needed to investigate genetic polymorphisms in HIV/AIDS. Regarding drug-using populations, of all the thousands of subjects enrolled in AACTG studies, fewer than 100 subjects were on methadone; therefore, a focus group will look at

PK interactions with methadone. A lead-in study is possible, to go through the steps of awareness and understanding before enrollment into a clinical trial. Finally, a trial is needed to examine pharmacogenomics to determine why different individuals handle the complicated HIV regimens differently.

Dr. Mildvan concluded her presentation by referring to the shared vision of her colleagues in the Underserved Populations Working Group and their desire to make inroads in the problem of getting at-risk populations into clinical trials.

Herman E. Mitchell, Ph.D., Senior Research Scientist, Rho Federal Systems Division, Inc., Chapel Hill, North Carolina

Dr. Mitchell presented information about the NIAID inner-city asthma study, one of the most intense efforts ever undertaken to study a chronic disease among inner-city children aged 4 to 9 years old. In the late 1980s, several investigators documented the rapidly increasing prevalence of asthma, especially among minority children in the inner city. Congress mandated funds to NIH to study the problem. Dr. Mitchell and his colleagues have studied more than 4,000 inner-city children over 15 years.

Dr. Mitchell's presentation focused on the first intervention study, in which 93 percent of the families were African American and Hispanic. He commented on the changing definition of target populations, including terms such as "minority population," "underprivileged," "disadvantaged," "underserved," and now "health disparities." Dr. Mitchell and his colleagues redefined the population under study as "inner city" because that was the language used by Congress. The definition of inner city is "contiguous census tracts in an urban area where 20 to 40 percent of the population is below the Federal guidelines for poverty." The inner-city population does not necessarily consist of minorities, but by definition the population is poor. The caretakers of children in this population were 96 percent female, and 62 percent of the children with asthma in the study were males.

In 1993, when the study was undertaken, 52 percent of the families included a household member with a job and 55 percent had incomes below $15,000, which was the Federal poverty level for a family of three. In 1999, with welfare-to-work programs, 74 percent of the families had jobs, but 60 percent of them were below the Federal poverty level. It was harder to recruit the families; they were now out working but not making any more money. Recent data show that, although poverty decreased for 24 years in this country, it has increased in the past 2 years, especially among African Americans.

The first notion was to do a broad-based epidemiologic study to identify factors related to asthma morbidity. The study found that many factors (access to care, insurance, continuity of care, family issues, compliance with care, cockroach sensitivity, psychosocial factors) are involved in the problem and there is no "silver bullet." Faced with all these factors, the researchers struggled with intervention design, specifically the question of whether to use nurse case managers or social workers. They ultimately

decided to use social workers because it was easier to teach a social worker how to do asthma care than it was to teach a nurse how to do social work.

The issue involves "the signal-to-noise ratio." As Dr. Mitchell explained, with so many things going on in the lives of inner-city families, when a physician or a nurse says, "You have to take your meds three times a day, and you have an appointment next Thursday at 5 o'clock," that message is drowned out. The system has to be changed; the noise must be reduced so that the message can be heard.

Study design considerations included an ethnographic committee and focus groups with the target population. During the focus groups, the participants suggested using the term "asthma counselors" instead of "social workers" and "program" instead of "research." Cultural consultants taught the researchers about the target populations. Experienced population researchers, project staff from the population, and pilot testing also became part of the design considerations.

Data collection bias included the social desirability response. A highly unlikely 96-percent medication adherence rate was reported, but subjects had difficulty with appointments. As a result, the clinics were opened at night and on the weekends. The study participants had needs that ranged from financial to health care to social support to legal, and the study had to find ways to meet those needs. Operational considerations included problems with safety for home visits. The researchers met with police to identify high-risk areas. Two home visitors were always sent out together, with a cell phone but without reimbursement money, and they always called right before the visit.

Other study design considerations included recognizing and designing to the population's needs. Reminders for appointments were necessary 2 weeks in advance, 2 days in advance, and on the same day. Transportation was provided. Flexibility in scheduling and rescheduling was necessary because 30 percent of visits were missed. Such flexibility applied to both staffing availability and design flexibility. A classroom setting is awkward for this type of asthma education, and 8 hours of education is too long. Therefore, the study resorted to 2 hours of education over two group sessions to introduce the study, followed by individual, one-on-one learning. In addition to transportation, babysitting was provided along with entertainment for siblings, incentives, and reimbursement. Participants were treated with kindness and respect. The number one reason participants continued in the study was that they liked the staff. After 2 years, the study had a retention rate of 96 percent.

The Inner-City Asthma Study, developed in the 1990s, had a strong, significant effect on asthma morbidity, an effect that continued through the following year. The study is now being implemented in 24 cities around the United States and is going on currently with thousands of families.

Discussion

The panel discussion raised the following issues and questions:

- A participant asked about the "thinking outside the box" idea expressed by Dr. Cargill and why in 2003 researchers still struggle to get people enrolled in clinical trials. Dr. Delgado pointed out that Dr. Zerhouni, in his Reengineering the Clinical Research Enterprise, stated that full participation in clinical trials is good science. Dr. Cargill pointed out that the problem with getting minorities into clinical trials occurs in the context of a larger issue—so-called "macrostructural forces." Investigators want a "clean" population to facilitate publishing papers in order to keep their jobs. Community-based organizations do not have the support to be able to document their work. Getting minorities into clinical trials requires that people work together to get past some of their own barriers. In addition, minority investigators must be trained, and that is an investment.

- Dr. Sidney McNarry, associate director of research infrastructure at the National Center for Research Resources at NIH, called the participants' attention to an untapped resource in this Nation in terms of recruiting and retaining minority participants in clinical research, namely, minority medical schools. Minority medical schools have credibility, faculty, and resources, and they should be offered membership on external advisory committees and boards. Dr. Delgado commented that everyone agrees with this assertion, but the people who need to hear it are not present.

- A participant from Beth Israel Hospital in New York remarked that the increase in the poverty level coincided with 9/11, when the economy dipped, and asked about the association between the two events. The participant also asked Dr. Fleckenstein whether biopsies were required in the hepatitis C study. When Dr. Fleckenstein said yes, the participant asked whether the biopsy requirement was a hindrance to accrual and whether patients were compensated. Dr. Fleckenstein responded that the biopsy requirement was not a hindrance to accrual because of the extreme efforts taken to provide free biopsies. The patients were not compensated, but the medicine and visits were free. Travel was not provided for patients, but childcare was offered. The participant also asked whether the Underserved Populations Working Group would include deaf people, disabled people, transgender people, and Asian Americans in addition to people of color and Hispanics. Dr. Mildvan responded that the community constituency group has asked that another member be added to the Underserved Populations Working Group from one of the mentioned populations that are at risk for HIV. The participant suggested that the study staff and PIs might want to play-act at joining a trial so that they can discover what it is like to be a patient participating in a study. A panel member reported that a number of community-based organizations have asked whether they can undergo mock participation in a clinical trial, and that activity has been initiated.

CONCURRENT BREAKOUT SESSIONS

Session I. After the Clinical Trial—Then What?

Discussion Leaders: Marian C. Limacher, M.D., Professor of Medicine, University of Florida College of Medicine, Gainesville, Florida, and Deneen Robinson, B.S.W., HIV Treatment Consultant, Dallas, Texas

Different Types of Clinical Trials and Implications for Post-Trial Management

Dr. Marian C. Limacher pointed out that some HIV-positive clinical trial participants have private health insurance, but because of fear of stigma and losing their employment, they do not use their medical insurance when seeking medical care. Instead, they enter clinical trials. Therefore, several issues involving people living with HIV necessitate various answers to the "then what?" question, and those answers are often unique to the individual who is participating in the trial.

Ms. Deneen Robinson added that for HIV patients, the clinical trial may be the major provider of medical care. Treatments for HIV often have not been used in the population; therefore, the purpose of the trial is to ensure not only that the product is safe but that it can actually work in combination with other drugs to treat HIV disease.

Researchers want HIV medications to do four things: (1) prolong quality of life, (2) limit the onset of opportunistic infections or life-altering diseases, (3) provide some reconstitution of the immune system, and (4) result in the least amount of toxicity damage to the person taking the medication.

If a person's main reason for going into an HIV trial is access to medical treatment, then a monetary incentive is unnecessary. Such people are willing to tolerate changes in how they look and feel because they are offered the opportunity to prolong their life. The research team takes on all aspects of medical care and provides medications not otherwise available. The participants are often people of color. Many newly infected men who do not have access to health care enter HIV clinical trials without understanding HIV disease and the impact of treatment on them. They are not adequately informed about other options, and if they opt to drop out of the trial, they know they will lose their access to health care.

In clinical trials involving chronic diseases such as cardiovascular disease, participants generally are of higher socioeconomic status than individuals who enter HIV trials, and their reasons for enrollment are altruistic as well as personal. They are interested in the benefits to future generations or other patients. They tend to have high levels of attendance, adherence, and retention. Staff involvement is less personal and there is a higher participant-to-staff ratio than in HIV trials.

Considerations at Trial Closeout and Study Termination

Clinical trials involve a broad spectrum of activities, and their timelines are highly variable. The phases of a clinical trial include concept development, funding, acquisition, protocol development and refinement, recruitment and followup, and closeout of the trial. However, these phases are not distinct—they overlap. Therefore, the planning for each phase must take place at the very beginning; communication, retention, and closeout and post-trial activity should be part of the early planning for a clinical trial.

Early planning meetings should cover what needs to be accomplished at trial closeout. First and foremost is acknowledgment of the value of the participants' contribution to the trial through a thank-you letter, certificate, or token of appreciation. Second, the participants should be provided with information about the trial results. The actual findings should be provided, if available, at the last visit, or they should be communicated to the participants by letter, phone call, or Web site. Conveying the results to the participants almost always involves some sort of mailing; therefore, post-trial funding is necessary to accomplish this task. Third, transition care to a nonresearch setting should be provided. The researcher should consider options for primary medical care for participants who need it.

Another consideration at closeout is maintaining a positive relationship between the participant and the research staff. It is important to remember that the main reason for good adherence and attendance in a clinical trial is the participants' relationship with staff. Maintaining a positive relationship also can be viewed as a recruitment tool for future research studies; participants can spread the word to others that participating in a clinical trial is a positive experience. One of the roles of a research clinic is securing populations for future studies.

A shift in the continuity of care occurs with the change from a protocol-driven practice to standard care procedures. Quality of care might decrease. Participants lose both their medical care coordinator—that is, the PI, the nurse practitioner, the social worker, or the case manager who makes referrals to other providers for various problems—and their access to care. In addition, the change in provision of medications means that medications will no longer be obtained regularly and easily even if there is some other way to pay for them.

The special issues at trial end include limited financial resources, lack of health care coverage, loss of "family" interaction and support of the clinical research staff, potential loss of medications, the lack of an alternative provider, reduction in quality of care, and concern about changes in clinical status.

Case Example: Lipid-Lowering Trial

The lipid-lowering trial involved patients with known coronary disease who were randomized to a statin or placebo. Followup occurred over a 4-year period. The closeout occurred as planned, and the preliminary findings were available at closeout. All the

patients had a personal physician throughout the study. The clinic visits documented outcomes and events, assessed lab work, and included physical exams. At closeout, letters were sent to participants and providers thanking them for their participation. The participants were invited to a group meeting to hear the preliminary study results and to learn what their participation revealed. They were "unblinded" at the time of the closeout, so they actually got to find out what medication they were on. They also were given a 3-month supply of medications because of the positive results of the study. The closeout event was well attended and well received. Participants were very satisfied with the whole experience, and many of them have enrolled in subsequent studies at the same sites.

Case Example: Women's Health Initiative

The Women's Health Initiative (WHI) study is ongoing, but the estrogen plus progestin arm of the hormone study was terminated early. The study began in 1993, and enrollment was completed in 1998 with a population of more than 16,000 postmenopausal women. The estrogen plus progestin arm was part of a large, complex WHI program. In May 2002, the Data and Safety Monitoring Board (DSMB) determined that the risks of breast cancer and cardiovascular disease events outweighed the benefits for active treatment with estrogen plus progestin. The DSMB determined that this arm of the study should close early. The recommendation was forwarded to and approved by the National Heart, Lung, and Blood Institute (NHLBI), and the director of NHLBI concurred with the recommendation.

Simultaneous with these events, the WHI Executive Committee drafted a paper with the findings, planned notification, and closeout, but the investigators were not notified until 1 month before closeout was to occur. The manuscript was published, and participants received notification on July 8, the day before the press release. They were told to stop their study medication and to attend a scheduled appointment. The result was an immense media response. Participants and providers called the clinics, and national organizations weighed in on the early termination of this arm of the study.

Overall, the participants appreciated being notified first and understood the process and the results. They realized that determining risks versus benefits was the reason they participated in the study in the first place. They felt proud to be "part of the answer." The participants were instructed to discuss further hormone treatment decisions with their personal providers, and all of them continued in the study for followup purposes. On the other hand, the health care providers and professional societies did not feel they had enough "warning" even though they had received annual letters describing the study. In addition, they failed to access the online manuscript in time to respond to individual patients' questions and were bombarded by non-WHI patients with questions, demands, and even lawsuits. Overall reactions criticized the study for not asking the right questions and for applying only to a few people. The industry response was to mobilize its forces to counteract the findings.

Lessons learned from the WHI experience include trying to anticipate media reaction, providing better and faster information to providers, engaging providers throughout the study to avoid "surprises," and paying attention to industry's potential response.

Case Example: HIV/AIDS

Ms. Robinson described two different case studies. One study took place in a community clinic setting where patients were recruited into the trial when they came to the clinic to access medical care. The trial site was in the same building as the clinic but on a different floor. The trial staff consistently tried to meet all the needs of the patients, including food and childcare. They also tried to provide support for participants' comorbidities, such as substance use, diabetes, and hepatitis C.

Once the trial was over, patients began to access care "downstairs" in the clinic, where they had to wait at least 4 hours to see a physician and where they did not get the kind of hands-on care offered "upstairs" at the trial site. Clinic patients had to go to a separate building to wait to pick up their medications. Other barriers involved income and transportation, both issues addressed by the trial but not by the clinic. Suggestions for improving the transition from trial site to clinical care include offering advice at the beginning of the trial for continuing health care once the trial is over, introducing patients as the trial is ending to the new clinic setting, and introducing patients to the care team or social worker they will deal with after the trial is over. If these suggestions are followed, then people who are no longer participating in a clinical trial would not have to learn how to navigate a new system on their own.

The second case study involves a white male in his 30s who was newly infected with HIV. He had no health insurance and no access to medications. He joined the trial in a private doctor's office because he wanted to get optimal care. Because of treatment failure, the patient switched to a new regimen. When that regimen failed, the individual was removed from the trial. He could not continue care with the private doctor because he could not afford to pay. He was forced to go to a community clinic, but he dropped out of care for a while because he was overwhelmed by the process of changing from a private physician to a community clinic. Suggestions for improving the lot of people as they transition from a clinical trial to standard care include offering a community educator for assistance, giving patients information about options, and providing patients with information for the health care provider. Following these suggestions will enable patients to make a smooth transition to the community clinic setting if they deplete their funds and can no longer afford care by a private physician.

Discussion

The breakout session raised the following issues and questions:

- Community advisory boards can play an important communication role at the end of a study, as well as during startup. Efforts should be made to keep them involved throughout the life of the trial.

- An attendee reiterated the importance of being prepared for trial closeout, including knowing how to handle timelines and negative findings from the Data Safety and Monitoring Board. Also, participants must be prepared for what happens at the end of a trial, not only for reentry into a clinic setting, but also for ending the trial relationships. In addition, followup through newsletters, phone calls, or e-mails should occur for individuals who fail the screening process for a particular trial but might be participants in future studies.

- Another participant suggested that psychologists be on hand to discuss the closeout process with HIV participants.

- Post-trial planning should entail merging research concerns with concerns about care. This notion should be added to research protocols, or a care plan should be included. Researchers do not think about care of the individual; they think about getting independent, objective data that will answer a specific aim or a specific objective. Researchers want to answer scientific questions, and care is seldom considered when planning a research study. This fact makes closeout, especially in HIV studies, very difficult.

- Another attendee asked a question about the phases of clinical trials: "What is the relationship between closeout and recruitment?" Closeout can mean the end of treatment, but it also can mean dissemination and enrollment in other clinical trials. Dr. Limacher agreed that closeout encompasses much more than just contact with participants; it includes dissemination of the findings and changes in practice. The planning for closeout should be part of the initial strategy. IRBs require that during recruitment, participants be told how they will learn—or if they will learn—the results of the study. Being part of the solution at the end is part of the recruitment process. Participants might be recruited into additional studies depending on whether other studies are available at the clinic and how the mechanism to maintain contact is funded and managed. Continuity can be planned.

- Another participant asked whether former trial participants can help to transition patients from the trial setting to the clinic setting. Speaking from his own positive experience, this participant noted the continuity of care he received as a participant in multiple studies at a clinic that is tied to a study site. Ms. Robinson noted that the examples she gave of HIV/AIDS trials concerned patients who tested positive and immediately entered a trial. In that case, the patients enter the research setting without establishing a relationship with the clinical care people. When the trial is over, they must make the difficult transition to care.

Session II. Minority Investigators in Clinical Trials—How Important Are They?
Discussion Leaders: Clemente Diaz, M.D., Professor and Chairman, Department of Pediatrics, University of Puerto Rico, San Juan, Puerto Rico, and Michele K. Evans, M.D., Deputy Scientific Director, Intramural Research Program, National Institute on Aging, NIH, Baltimore, Maryland

Dr. Clemente Diaz presented the Hispanic perspective on the importance of minority investigators in clinical trials. The underrepresentation of minorities in clinical trials resulted in a 1993 congressional mandate that led to the NIH policy on inclusion of women and minorities in clinical research. There is a need to understand how history, attitudes, cultural beliefs, social issues, and investigative behavior actually affect the enrollment of minorities in clinical trials. The NIH policy resulted from a response to ethical principles of social justice and the need to balance research burdens and research opportunities and benefits across society.

Minority Researchers: How Are They Effective?

Dr. Diaz stated that minority researchers are effective because they are part of the community and, therefore, function as access points for minority populations to participate in research. Sometimes minority researchers work in settings that are isolated in terms of minority representation; therefore, they are key to accessing research for minority populations. Minority researchers offer a cultural empathy, which acts as a bridge to minority participants. Minority researchers also know the communities that are advocates for minority populations and have negotiated good relationships with organizations that offer access points to these minority populations. Strong bonds with community-based organizations can lead to partnerships to enhance not only enrollment but also retention and involvement. In addition, by role modeling and mentoring, minority researchers foster and promote increasing numbers of minority researchers for the future. Minority students may be reluctant to choose research as a profession because of the lack of financial incentives. Therefore, when minority researchers act as mentors, they become instrumental in helping to increase the number of primary investigators.

Hispanics as Participants

Dr. Diaz focused on the heterogeneity of the Hispanic population. Hispanics comprise Mexicans, Puerto Ricans, Cubans, South and Central Americans, and Spaniards. Although Hispanics share certain values and a language, there are significant differences among them. Researchers must recognize these differences in order to successfully enroll Hispanics in clinical trials. In many instances, issues of trust, language, religion, and cultural beliefs affect how research is perceived by Hispanics. This population must perceive the benefits and value of research, especially regarding high-prevalence conditions that indicate health disparities, such as HIV/AIDS, tuberculosis, breast and cervical cancers, cardiovascular diseases, asthma, hypertension, and diabetes. For example, asthma is extremely prevalent in Puerto Ricans, and diabetes is an increasing problem for Hispanics. Because Hispanics perceive these issues as relevant, they will be interested in participating in clinical trials in these areas.

Health issues and disparities in Hispanics raise some political issues. Language and acculturation are important for Hispanics, and the issues are very different for the first generation, second generation, etc. Likewise, gender role issues are important; men and women have different health care behaviors. Hispanic men tend to disregard as a waste of time preventive health care behaviors such as yearly physical examinations. Hispanic women postpone preventive care because of their role as caregivers for family members and children.

In addition, decisionmaking in the family is important. For Hispanics, that fact translates into difficulties in getting informed consent; Hispanic people need time to discuss informed consent with family members. In general, Hispanics have less access to health insurance, which limits their access to preventive health services. They also lack access to public health education materials, for example, vaccination information.

There are also differences in trust, reactions to medication, and perception of pain; therefore, an individual approach is often necessary. Questions will arise regarding access to urgent care and to emergency room services, perception of pain and threshold of pain, and recognizing and reporting adverse events—all critical issues for clinical trials.

Promoting the Inclusion of Minorities in Clinical Trial Research

Some general principles and elements that must be present to promote the inclusion of minorities in clinical research are as follows:

- Existence of active links with grassroots organizations
- Outreach and awareness of the cultural component that leads to minority-relevant research
- Knowledge of motivations for participation, that is, the perceived value of the study, the altruistic component, the desire for peer interaction, and access to care
- Education importance and rationale for participation in clinical trials
- Accessible sites and convenient hours
- Knowledge of the role of the family in decisionmaking

Promoting the inclusion of minorities in clinical trial research is important because the United States has one of the most ethnically diverse populations in the world. A third of the current U.S. population belongs to minority groups, and this proportion is expected to increase steadily. By the early part of the 21st century, today's minority groups are likely to make up more than half of the U.S. population. Information gathered from these populations will be essential for the implementation of health policies and interventions in the future.

The barriers to promoting inclusion of minorities in clinical trial research fall into three general categories:

1. Simple logistical barriers, such as transportation, meals, child or elder care, and time of visits
2. Complex logistical barriers, such as fear of large institutional settings, lack of cultural diversity in the staff, and recruitment and instructional materials in an inappropriate language or at inappropriate literacy levels
3. Barriers related to attitudes, beliefs, and insufficient knowledge, such as fear or distrust of research; lack of familiarity with research procedures such as randomization, masking, and placebo controls; and fears or concerns about interference with primary care or continuity of care

Investigators must recognize the obstacles to minority participation and develop approaches to overcome them. The barriers can be broken, and minority participation can be made more accessible in a number of ways:

- Have members of the target population visit the clinic.
- Hire appropriate staff.
- Understand the need for cultural sensitivity training.
- Include community involvement in the planning process to ensure appropriate language and literacy level.
- Recruit credible spokespeople.
- Seek communication with and endorsement by community leaders.
- Avoid jargon.
- Emphasize benefits gained through participation.
- Ensure a clear understanding of the agendas of the investigators, community, and participants.
- Maintain credibility by never promising what cannot be delivered.
- Never promote activities before they are ready.

The roadmap to success in promoting inclusion of minorities in clinical trial research is characterized by an essential understanding of the target population, including understanding the differences and diversity among subcultures in the Hispanic community. Also, the roadmap to success involves knowing the structure of the community, the process whereby health policy decisions are made, and the opinion makers within the community. In addition, success depends on the recruitment of credible spokespeople, knowing what constitutes a family in the target population, and understanding how decisions are made within the family. Effective means of communication with the target population are through religious organizations, through printed materials and presentations, and through word-of-mouth given by research participants or community advisory board members.

The following practical tips have proven successful:

- Spend time in the community.
- Do library research on medical and scientific literature related to the target population as well as census data, government reports, maps, and newspapers.
- Consult with experts.

- Establish specific goals for recruitment and retention.
- Offer monetary incentives, if necessary.
- Ensure that the investigators, staff, and community understand the design, methods, implementation, and completion of the study.
- Identify individuals or groups that can give access to the community.
- Set up advisory boards to review research plans, informed consent, and recruitment and retention.
- Transmit the research findings back to the community.
- Develop a Web site.

Women and Infants Transmission Study

Dr. Diaz concluded his presentation by describing the NIAID-funded Women and Infants Transmission Study (WITS), a multisite observational study designed to examine the impact of HIV infection on HIV-infected women and their infants. Prospective clinical and laboratory data on HIV infection and disease have been systematically collected at specified intervals from mothers and infants at six sites in the United States: Boston, Chicago, Houston, New York (two sites), and San Juan, Puerto Rico. As of July 2003, WITS had recruited 3,042 women and 2,550 children. The participant distribution is 49 percent African American, 34 percent Hispanic, 12 percent white, and 5 percent others. At all sites, WITS has become the model for successful prevention of mother-to-infant transmission of HIV. In Puerto Rico, the expansion of WITS strategies across the island has achieved a reduction in the number of infected infants from 150 in the 1980s and 1990s to 1.2 in 2003. There have been no infected infants born in the program since 1996. In addition, this highly successful program has achieved long-term retention and continued enrollment.

Dr. Diaz ended by stating that promoting ethnic, racial, and gender diversity in clinical research helps to address gaps in social justice, to end health disparities, and to represent all segments of a multiethnic society. It should be a goal for the 21st century.

The Role of Minority Investigators in Developing Diverse Cohorts in Clinical Research

Dr. Michele K. Evans spoke on the importance of minority investigators. She began by citing the influence of ethnicity, socioeconomic status, and age on health. Health disparities affecting African Americans and Hispanics are evidenced in renal transplantation rates, renal replacement therapy morbidity, evaluation and management of chest pain, treatment of early-stage lung cancer, acute myocardial infarction mortality, access to invasive cardiac procedures, outcome of left ventricular dysfunction, cancer treatment in clinical trials settings, and treatment of pain related to terminal disease.

The sources of health disparities are complex. They are rooted in historic and contemporary inequities related to health care systems, administrative and bureaucratic processes, utilization managers, health care professionals, patients, and clinical and basic biomedical researchers. An Institute of Medicine report on unequal treatment found that racial and ethnic minorities tend to receive lower quality of health care than

nonminorities regardless of access factors such as medical insurance and income. Factors that help to explain this disparity include the operation of health care systems, the legal and regulatory climate, discrimination, biases, stereotyping, uncertainty, and patients' cultural preferences. Biomedical researchers contribute to this problem by failing to research disease states that are relevant to minority populations. Unequal treatment leads to the inability to get people to participate in clinical trials.

Of 23,208 full professors teaching in U.S. medical schools, 29 are Native American. Dr. Evans pointed out that the country clearly needs more than 29 people to drive the research infrastructure to look at problems such as diabetes, alcohol abuse, and mental health disorders in the Native American population.

Minority Clinical Researchers: Barriers and Responsibilities

How does a minority in the medical sciences decide to become a researcher? One barrier to that decision is the lack of financial incentives, which are greater in clinical medicine than in basic or clinical biomedical research. Instead of careers in research, minority physicians often enter private practice and become active in community affairs. Minorities in the medical field also need endorsement and encouragement to decide to pursue basic or clinical biomedical research as a valid career choice. Once the choice has been made to enter the field of clinical research, the researcher needs further endorsement to take up minority health and health disparities as a valid research discipline. An additional disincentive is the number of NIH grants given to minority investigators.

In the face of all these barriers, minority researchers bear a responsibility that involves "the vision thing"—they have the ability to bring personal life experiences and perspectives to research. Dr. Evans described an epidemiologic study she is conducting in Baltimore. The study is looking at the effects of race and socioeconomic status on issues of health disparity in a city that has some of the worst health statistics in the Nation. As a medical oncologist who does basic biochemistry of DNA repair in the laboratory, Dr. Evans admits that she lacks the knowledge of an epidemiologist, but she is driven by "the vision thing" to survey 40,000 households in Baltimore to discover the reason for the city's terrible health statistics. "The vision thing" also may explain why underrepresented minority faculty members are 3.2 times more likely than white faculty members to serve on institutional review boards.

Investigators must address barriers to participation in clinical research for themselves as well as for the participants they hope to enroll in the studies. To a minority investigator, clinical research might entail the involvement of social services and an ethical component in the treatment of underserved populations. Research also must be relevant to the perceptions of the participants, and it must address what the researchers want. In addition, environmental logistics must be addressed, including multiple changes of address, the reliability of telephone numbers, lack of transportation, safety issues, childcare, confidentiality, the type of study, and economic concerns.

It is possible to negotiate the barriers to participation of minorities in clinical research by taking the following steps:

- Approach participants through community organizations, such as local churches, tenant associations, neighborhood civic associations, and police departments.
- Take a face-to-face recruitment approach.
- Use researchers of the same race and gender as the participants.
- Create a sense of investment in the study.
- Design the study with a nonresearch benefit for participants.
- Establish a network for participant referral for medical and nonmedical issues.
- Study staff selection based primarily on skill level, followed by diversity.
- Ensure that the spokesperson for the study in the community is a well-trained lay community coordinator, not the principal investigator.
- Offer compensation for time, free transportation, and flexible scheduling.
- Publish a newsletter with study updates, health education information, and features on staff and participants.
- Devise mechanisms for participant feedback.
- Use health fairs, street festivals, and social events to enhance a sense of community.
- Establish contact with participants by phone, mail, or reports.

Setting the Tone for Research: Cultural Proficiency Curriculum

Some medical schools address the issue of the legacy of distrust and attempt to introduce researchers to the notion of cross-cultural communication. A cultural proficiency curriculum teaches the recognition of and appropriate response to key cultural features that affect clinical research and clinical care. The curriculum presents important factors that influence the way health care is delivered and clinical research is conducted. Cultural factors influence the ability to deliver health care and to conduct clinical research. Columbia University, the University of California at San Francisco, and Rush Medical College have developed cultural competence courses for medical students and residents.

Cultural proficiency courses present the scientific rationale for inclusion of underserved populations and minority groups in research projects and for changing the diversity dynamics nationwide; for example, a study of African American culture and clinical research reveals a legacy of mistrust. Cultural proficiency courses also describe and explain the need for cultural competence and sensitivity among clinical researchers and introduce researchers to cross-cultural communication. In addition, the concept of cultural humility and the role of advisory boards are covered topics. Moreover, the courses provide a background for investigators to develop a framework for effective community-based research.

Setting the Research Goals: Operational Goals and Objectives

The operational goals and objectives should include the following:

- Enhancing training opportunities in epidemiology, aging, and health disparities research for local students pursuing careers in public health
- Enhancing participation of minority investigators and minority institutions in clinical research and contributing to building research capabilities at minority institutions
- Developing effective community-based methods of recruiting and retaining minority and socioeconomically diverse participants in clinical research

The role of community advisory boards includes offering advice and counsel, giving consent, building larger communication networks within local neighborhoods, changing perceptions that have inhibited development of substantive working relationships between community members and scientific researchers, and reaching a larger segment of the community for research participation and dissemination of health findings and preventive methods for reducing risk.

Community advisory boards consist of 6 to 28 members who meet 2 to 12 times per year. Membership on community advisory boards can include clergy, school officials, tenant association members, neighborhood residents, politicians, community health professionals, and neighborhood associations.

Questions to be answered on the topic of minority investigators in clinical trials include the following:

- How can the number of minority clinical investigators be increased?
- Why are minority investigators critical for the successful recruitment of diverse subjects?
- What can nonminority investigators do to improve participation rates among diverse segments of the population?
- What is the role of minority and community-based health care providers?
- What is the role of community institutions in recruitment?
- Should investigators design research studies with specific goals and benefits that may appeal to a diverse cohort?
- Is cultural proficiency a factor in clinical research?

Discussion

The breakout session presentation by Drs. Diaz and Evans prompted the following discussion:

- A participant commented on a presentation she attended during which a minority investigator gave a careful and thorough explanation of a study, including the informed consent process.

- Another attendee posed two questions: (1) How are female care providers and/or researchers perceived, supported, and/or undermined by the general Hispanic population? and (2) What is meant by cultural humility? Dr. Diaz responded to the first question by saying that female care providers must be aware of underlying issues, such as childcare, and biases and must be able to bridge the language gap. In response to the second question, Dr. Evans explained that minority investigators must accept the lifestyle of minority participants in clinical trials even though they may not identify with that lifestyle. This type of acceptance is basic to understanding how to reach the populations that most need to participate in clinical research to get access to decent health care.

- The attendee offered a proposal to train more Native American and Hispanic nurse midwives and nurse practitioners to be investigators and to take part in clinical research nationwide.

- Vicki Cargill, from the Office of AIDS Research, offered two points: (1) both minority and nonminority researchers have something to offer in the investigation of health disparities and (2) outreach educators from the community must be offered a fair staff salary. Dr. Diaz concurred that outreach educators often make invaluable contributions to the success of trials.

- Another participant requested talking points on the spiritual or humanistic component of research and on the need for a systematic approach to building an infrastructure in medical education to enlarge the pool of minority investigators.

- Another attendee asked about the concept of building trust in African American and other minority communities with clinical researchers. Is it possible to create trust between the two parties when there has never been a foundation of trust? The attendee asked Dr. Evans if her curriculum covers this issue. Dr. Evans responded that her curriculum addresses the issue of trust from the point of view of the staff, investigators, and participants in a clinical trial.

- Another attendee asked if Tuskegee is the only type case used to examine the issue of mistrust in clinical investigations. Dr. Evans replied that the discussion always begins with Tuskegee.

- Dr. Herman E. Mitchell, from Rho Federal Systems Division, asserted the importance of minority investigators educating nonminority investigators. Dr. Diaz agreed that this type of education is important. Issues of trust are incredibly complex and go far beyond minority issues. They concern medical care and the relationship between patient and practitioner at every level.

- Another attendee asked about promoting clinical trial participation among rural minorities and using local practitioners as co-investigators. Dr. Diaz agreed.

Session III. Role of the Community Advisory Board and Outreach Activities

Discussion Leaders: Anne Madey, R.N., Research Nurse Coordinator, University of Tennessee Health Science Center, Memphis, Tennessee, and Matthew Murguia, Director, Office of Program Operations and Scientific Information, Division of AIDS, NIAID, NIH, Bethesda, Maryland

Ms. Anne Madey is the research nurse coordinator for the NIAID study titled "African American and Caucasian Response to the Standard Therapy for Hepatitis C," which involves the treatment, followup, and side effects of the standard therapy for hepatitis C sequelae. Her presentation described her work on another project—a hepatitis C screening and education program in the Memphis community, which involves interacting with a community advisory board. Ms. Madey focused on the following question: What is the connection between a health care provider and the community in which he or she works? Her presentation offered facts and demographics about Memphis and its population, described the University of Tennessee's commitment to the community, and gave detailed information about elements of the model program.

Facts and Demographics

Memphis is the 18th largest city in the United States, with a population of about 661,000; however, the population of the metropolitan statistical area is about 1.1 million. In Shelby County—where the city of Memphis is located—the African American and Caucasian populations are evenly distributed at about 48 percent, with Asian/Pacific Islanders and others at 3.2 percent. In terms of employment, the population is 40 percent blue collar and 60 percent white collar. Thirty percent of the jobs are service oriented, 18 percent are in the retail field, 14 percent are government related, 12 percent involve transportation and communication, and 11 percent are in manufacturing. The highest educational level attained for 30.7 percent of the population is high school graduate, and 15.3 percent of the residents have bachelor's degrees. The median age of the population is 33, and the average annual salary per household is close to $40,000.

University of Tennessee's Commitment to the Community

The University of Tennessee mission statement calls for involvement with business, industry, and local, State, and Federal governments to facilitate programs and services for the community. The university's health career programs reach out to African Americans to promote interest in health care research beginning at the elementary level and continuing through postbaccalaureate studies. Ms. Madey also mentioned the efforts of the Office of Special Events, the Communication and Marketing Departments, and the Seeds of Discovery program, all of which testify to the university's significant community outreach efforts.

The Hepatitis C Screening and Education Program

Ms. Madey provided some information about the hepatitis C virus (HCV) for the laypersons in the audience, noting that 85 percent of the people who contract the virus

will develop chronic liver disease. HCV is the major reason for liver transplants. Called "the silent killer," the virus can be present in the body for up to 30 years before it presents symptoms. About 4 million people in the United States have tested positive for antibodies to HCV. The rate of HCV is higher in African Americans than in whites—about 3.2 percent versus 1.5 percent, respectively. The replication of the virus is higher in African Americans than in whites, and about 10 percent of African American men between the ages of 40 and 49 have tested positive for HCV.

Ms. Madey described the model screening and education program for HCV at the University of Tennessee. She discussed the program's goal, objectives, and purpose; population identifiers; information dissemination; implementation; and evaluation.

- *Goal, objectives, and purpose.* The goal of the screening program was to provide education about the disease. Children are vaccinated against hepatitis A and B, but there is no vaccine for HCV; therefore, education is key to preventing the spread of the disease and making people aware of the treatment options for those who have contracted the virus. Launching a screening program for HCV requires both interaction with the community to be screened and fostering a working relationship with health care providers.

- *Population identifiers.* An organization called "Memphis Healthy Churches" was instrumental in helping to arrange for nurses and nurse practitioners to conduct screenings. Focus groups also were used to identify populations to be screened, as were community centers in neighborhoods. The number of screened individuals at group sites or functions was low at first because of people's resistance to having their blood drawn.

- *Information dissemination.* The dissemination efforts were successful because many individuals in the community do not have access to health care or a one-on-one interaction with a health care professional.

- *Implementation.* Implementation of the screening program required coordination with a phlebotomist and a medical laboratory to get free HCV antibody screens. Many people were afraid to have their blood drawn, and personal attention and discussion were needed to address issues such as confidentiality and distrust of medical personnel. In addition, the program offered followup care.

- *Evaluation.* One of the ways to evaluate the program's success was to consider the trust issue. Time and cost were other issues to be considered. Adjusting the screening schedule for the convenience of the participants was crucial. Ethical issues and confidentiality also were key concerns. Regarding future programs, Ms. Madey announced a plan to screen the Shelby County jail personnel who work with prisoners.

Community Advisory Boards

Mr. Matthew Murguia began his discussion by defining what a community advisory board (CAB) is. The community component of a CAB involves those members of a community who are either infected or affected by a particular disease and in need of clinical or research intervention. The community can include current and former clinical trial volunteers, national organizations, family members with infected relatives, health care professionals who serve and treat the participants affected by the disease, and vulnerable populations such as children, pregnant women, the elderly, the medically underserved, and the transgender community. The definition must be flexible enough to fit the needs of the population being researched and inclusive enough to reflect where the research is being conducted.

The advisory component of a CAB involves the board's role in providing input and guidance in all aspects of clinical trials. CABs provide guidance, but they do not have any legal or formal authority to require changes in a trial or how it is implemented.

The Mission of a Community Advisory Board

The CAB's mission is to decide what role it should play in the community and, ultimately, in the clinical trial. For the most part, CABs ensure that the needs of the community are considered in all matters regarding the provision of research-related care, program management, and the establishment of the scientific agenda. Mr. Murguia stated that the last point often causes an interesting dilemma for the CAB and the principal investigator. Researchers coming into the community may want to carry out certain tasks within the study that the community does not fully understand. A balance must be struck between the CAB and the principal investigator when establishing the scientific agenda for the trial.

Mr. Murguia gave an example of a mission statement from a CAB in Washington, DC, the Capital Area Vaccine Effort (CAVE). The mission statement reads as follows: "CAVE is a volunteer panel of individuals from the general public and from the diverse communities affected by AIDS. CAVE is organized to assist and advise AIDS vaccine trials in the metropolitan DC area." The key words used in a CAB mission statement are "volunteer," "diverse," "assist," and "advise."

A CAB such as CAVE wants to assess the concerns of the community it represents and to serve as an advocate for individuals in the trial and the general public as a whole. A CAB acts as a liaison and ombudsman between researchers and those interested in the research. As part of its mission statement, the composition of a CAB reflects the affected populations it represents. As appropriate, a CAB encourages participation in clinical trials and acts as a community educator. A CAB also assesses the ethical and social implications and the impact of a trial.

The Functions of Community Advisory Boards

CABs carry out the following functions:

- CABs serve as the eyes and ears of the community regarding the conduct of research. They are the main link between the researchers and the community. Their members are from the community and know about the community.
- CABs represent the trial volunteers in interaction with the site staff. They engage in conflict resolution, discuss volunteer retention issues, and provide insight into how sites are managed.
- CABs provide advice on all aspects of conducting a clinical trial, including identifying research priorities, reviewing the protocol to ensure it is written in plain language or in the native language of the participants, monitoring the informed consent process, dealing with ethical issues, and advising on standards of care.
- CABs serve as information sources, ambassadors, and liaisons to staff and volunteers. They help foster a supportive environment, serve as mentors to new CAB members, and provide legitimacy to the research site.
- CABs help build trusting relationships in the community. They can serve as a sounding board for community members, provide recruitment advice, and ensure that the site conducts all activity in a culturally and linguistically appropriate manner.

Community Advisory Board Activities

Mr. Murguia explained the types of activities that CABs engage in. CABs can help researchers focus their message by suggesting outreach activities, such as community forums, town halls, and brown bags. They also can suggest materials development, including the production of brochures, factsheets, flyers, and print and radio advertisements, and they can review the materials to ascertain whether they are readable, understandable, and written at the right level of education. CABs also can determine the appropriate educational level for the community and define what the community already knows.

CABs also can be involved in information sharing about the trial with other concerned community advocates by writing letters to the editor and newsletter articles and by pursuing other avenues for informing the community about participating in research. In addition, CABs can serve as media resources by helping research investigators to focus their messages, develop advertisements, and place their ads. CABs act as liaisons to other communities.

Mr. Murguia emphasized that CABs are made up of volunteers. As volunteers, they may have full-time employment, children, and transportation needs. Monthly attendance at CAB meetings, workshops, and brown bags takes time away from their families and other activities. Therefore, researchers must be aware of the fact that CAB members are not recruiters. CABs can have a significant impact on the effectiveness of researchers in the community. If a CAB does not support the proposed research in a given community, it can effectively shut down the investigators' recruiting efforts.

Mr. Murguia added some information about CAB membership. He reiterated that CAB membership reflects the diversity of the community being researched and the community in which research is being conducted. The selection of CAB members should include considerations such as race/ethnicity, gender, sexual orientation, age, the language skills of the individuals and the language they use or feel most comfortable using, educational levels, economic status, religious/medical communities, advocacy groups, and social and fraternal groups. Fraternal groups have strong historical linkages to the communities, are positive beacons of change, and are respected in the communities. They can serve as a useful resource in disseminating messages. Other considerations for inclusion as CAB members are sex workers, injection drug users, prisoners, and students.

Components of a Successful Community Advisory Board

Mr. Murguia explained that a key factor in the success of a CAB is the principal investigator's (PI) involvement and commitment, which can be assessed by answering the following questions:

- Does the PI attend CAB meetings?
- Is the PI easily accessible to answer questions?
- Is the PI visible in the community under study?

Another component of a successful CAB is the existence of clearly defined missions, goals, roles, and bylaws. It is essential that people understand the roles of the CAB. Diverse membership also is extremely important to the success of a CAB; difficulty in recruiting volunteers for CABs can compromise the board's diversity. Another concern involves ongoing support for the CAB; funding is paramount for the successful management of a CAB.

CABs need strong meeting support, which includes a clear agenda, regularly scheduled meetings with advance notice, and sufficient funds for travel reimbursement, if allowed. Successful CABs produce meeting minutes and provide information with adequate time for review. Administrative support should be provided for the CAB, and food and refreshments should be supplied.

Finally, CABs should have planned training activities that encompass orientation and mentoring of the CAB members. The training should cover the terminology of the clinical research trial and a general overview of the science involved in the study.

Parity, Inclusion, and Representation

Mr. Murguia ended his presentation with some comments about parity, inclusion, and representation:

- *Parity* calls for CAB members to be actively involved in the process so that everyone has the same information and understands it at the same level. Parity may be a new concept to some, but it has been well documented in the AIDS scientific and

advocacy communities. The only way to achieve parity is through training, workshops, informational exchanges, and asking questions.

- *Inclusion* means that all those who have a stake in the issue should be at the table when decisions are made. These stakeholders are individuals who are most affected by the disease or study and are representative of the community as a whole and of the community being researched.

- *Representation* means that each person should have an equal voice at meetings. No one person should dominate.

Mr. Murguia concluded by listing the following learning points: (1) community input is a must in research, (2) CABs are an integral component of research, (3) CABs must have clearly defined roles, (4) ongoing support of CABs is essential in terms of both money and staff time, (5) diversity in membership is a must, and (6) CABs vary in what they can and are willing to do depending on their location and membership.

Discussion

The breakout session presentations by Ms. Madey and Mr. Murguia prompted the following discussion points:

- An attendee commented on the difficulty of including parity, inclusion, and representation (PIR) in CABs. Inclusion can be facilitated by guaranteeing a convenient time and place for meetings or by offering stipends for cab fares. The representation component of PIR necessitates an examination of the ability of community members to participate on a CAB. The parity component is involved if members of the CAB disagree about a recommendation or advice given to the research site.

- Another attendee mentioned her experience as chair of a CAB in Cleveland. On the issue of parity, she stated that an important strategy is for the investigators, the trial patients, and the community to agree to disagree with each other. The issue of parity must be addressed to defeat institutional racism; in fact, women, especially Latina women, should be part of CABs. Building parity and seeking inclusion are worthwhile activities.

- A participant described the difficulties involved in recruiting Hispanic community members for CABs in areas with a high proportion of Spanish speakers. The difficulty arose because staff members lacked the ability to speak Spanish. A PI capable of speaking Spanish, as well as translators, can meet with community groups to recruit CAB members. Letters and announcements do not work as well as personal contact.

- Another participant, with extensive involvement with CABs, reiterated the importance of attending community meetings to recruit qualified CAB members,

including women and African Americans. A problem was the lack of inclusion of Caucasian or Hispanic members on the CAB. In addition, CABs often do not realize how much power they actually have. CAB members must voice their opinions and refuse to be conceived of as tokens; instead, they must feel like they have ownership of the CAB.

- An attendee called attention to the fact that an individual can be bright and insightful but not necessarily literate. It is a challenge to find a way to include such individuals on CABs.

- A participant remarked on two significant barriers to CAB participation at the Adult AIDS Clinical Trial Group at Duke University. One barrier concerns negative media attention, which has been offset by the community activities of its large, diverse CAB. The other barrier is staff turnover, the effects of which can be avoided by having more than one staff member do outreach in the community.

- A participant from the HIV Vaccine Trials Network made three points about CABs:

    1. Research organizations should provide training for PIs to learn how to work with communities just as they provide training for CAB members to understand scientific terminology.
    2. CABs can engage in community consultation. For example, if the research involves 18- to 25-year-olds, but no one from that group can be found to sit on the CAB, the CAB members must consult with 18- to 25-year-olds in the community.
    3. CABs should build into their structure the people they want to consult with, and they should put community issues at the top of their agendas.

- An attendee from the Capital Area Vaccine Effort pointed out that to ensure diversity, the CAB meeting location can rotate. Depending on the location, a very different CAB might emerge. Also, CABs are powerful and can close down sites, but their goal is to promote research. The question remains about how to ensure community representation.

- An attendee from the HIV Vaccine Trials Unit at Johns Hopkins University (JHU), who is the community liaison for the CAB, reported that the JHU CAB uses an annual schedule of 3-month rotating meeting locations. As a result, the CAB is able to move around in the community and pick up a person or two from each of the locations. Parity, inclusion, and representation are assessed every 3 months through a unit evaluation by the CAB to determine what populations should be added.

- A participant posed some questions about the connection between community advisory boards and the actual increase of diversity in clinical trials. Does increasing diversity in the CAB automatically result in an increase in diversity in the clinical trial? What are some of the specific steps that a CAB can take to increase diversity in

trial participants? Diversity is a key piece of a CAB, but what are the other pieces that contribute to getting more people from different walks of life to participate in a trial and stay through until the end? Mr. Murguia asked whose role it is to carry out these tasks: the CAB's role? the community educator's role? the recruiter's role?

- Another participant reiterated the importance of the community outreach aspect of a CAB.

- An attendee from Family Health International, referring to the definition of community, stated that researchers often use the CAB to conceptualize a target population instead of thinking of target populations as objects of research and communities as separate entities. People who enter clinical trials come from a wide range of communities. The issue is really trying to figure out where they are coming from, who the stakeholders are, and how to work together as a group. Defining a community is not more important than discovering who the people are, where they are from, and what their values are. Ms. Madey responded that the question might be as follows: Is the disease the community or is the community the disease? "Community" is difficult to define.

- A participant described a Title IV CAB that she chairs in St. Louis. The trial began with women, children, and youth, and the CAB comprised 8 to 10 people, many of whom did not understand the role of a CAB. The CAB members were educated about physician services, clinical services, and the need for further recruitment for the CAB. A binder of materials disseminated in clinics, an eight-page newsletter published every 3 months, meals, cabs, and childcare were provided. The CAB listened to participants' complaints and brought them back to the investigators. The CAB has expanded its diversity and has been successful at retaining its members.

CLINICAL TRIALS RESOURCES

Wilma Templin-Branner, M.S., Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee

Ms. Wilma Templin-Branner demonstrated the electronic Clinical Trial Resource Guide, which provides clinical researchers and other health professionals with information about the clinical trials resources of NIAID and other Federal agencies and private organizations. The information in the guide can help investigators to identify and retain individuals in clinical trials, particularly individuals in minority groups. Ms. Templin-Branner also demonstrated a sampling of the Web sites and databases included in the resource guide that can be used to (1) identify relevant clinical trials, (2) identify human subject policies, (3) obtain information about funding sources and mechanisms, and (4) learn how to prepare successful grant applications.

The mini-CD includes topics that range from appropriate human subjects policies to clinical trials databases, a race and ethnicity bibliography, cultural competence in health care, diversity in clinical trials, funding, general clinical trials Web sites, HIV/AIDS clinical trials Web sites, PubMed, resources for diversity in clinical trials, and women's

health. Each of the topics on the CD is linked to Internet resources that are considered the most inclusive and reliable sites on the topics. The sites were compiled by the Office of Special Populations and Research Training, the symposium steering committee, the symposium speakers, and the Oak Ridge Institute for Science and Education. Ms. Templin-Branner asked symposium participants to e-mail her other sites that should be included (templinw@orau.gov).

Ms. Templin-Branner pointed out some of the information available on each of the topics, including factsheets and order forms, computer-based training, ethical guidelines, journal articles, a grant application tutorial, and an HIV/AIDS database. She emphasized that the Resource Guide is intended to be as comprehensive and inclusive as possible in presenting information on increasing diversity in clinical trials, finding information on specific populations, and attracting and retaining minorities in clinical trials. She demonstrated a search in PubMed and ClinicalTrials.gov.

WHY PRIMARY CARE PHYSICIANS DON'T REFER THEIR PATIENTS TO CLINICAL TRIALS

John Hogan, M.D., Medical Officer, Unity Health Care, Inc., Washington, D.C.

In explaining the type of organization he represents, Dr. John Hogan stated that Unity Health Care in Washington, D.C., is a large conglomerate (23 sites) that started as Health Care for the Homeless and two public health clinics. Principal investigators from a clinical trial supported by NIAID provide care for HIV patients at Unity Health Care. The clinic's patients come primarily from Vietnam, Latin America, the Caribbean, and Africa.

Dr. Hogan explained that he polled his colleagues to arrive at an answer to the question of why primary care physicians do not refer their patients to clinical trials. **The basic problem is a deep-rooted distrust of the health care system**, which has existed for many years. The problem originates with patients who do not have direct access to research institutions and physicians who do not work in them.

A caring community physician who has worked hard to dispel his or her patients' basic distrust of the system and then agrees to refer patients to a clinical trial often wonders what is going to happen to them when they get there. The referring physician often must deal with the patients' fears regarding clinical trials. In addition, the physician has to monitor patients' behaviors and fears while they are in the clinical trial.

Dr. Hogan examined the root of this distrust and some truths, myths, and legends associated with it:

- *Truths.* The Tuskegee Syphilis Study and the U.S. military's use of LSD on soldiers were trust-breaking occurrences. The only way to repair the broken trust that resulted from these mistakes is through time and consistency.

- *Myths and legends.* There are Web sites that claim that HIV is a virus made by scientists, pharmaceutical companies, and American physicians as an agent for

African American genocide. Another belief is that HIV medications cause all the symptoms of AIDS and HIV infection; therefore, the HIV virus does not exist and the medications should not be taken.

A moral issue is involved in the topic. Patients should have access to health care through participation in clinical trials. The ethical dilemma involves the situation of the have-nots who are desperate for access to health care and researchers who are interested primarily in advancing science through their trials. Unfortunately, not enough physicians or health care workers view the disenfranchisement of patients who have little access to medical care as a moral issue. Those who do are stretched very thin.

Common reasons that providers give for not referring their patients to clinical trials include (1) not having time because they are too busy trying to "pay the bills," (2) not having time to keep up with what is available or to research the studies, and (3) not having the staff to do the research. They also claim that they forget to refer their patients.

Educating the Provider

Physicians must be alerted to the fact that they need to learn about clinical trials for their patients' sake. Many of them need help in realizing the possibility and the importance of patients getting medical care through participation in trials. In addition, physicians must be encouraged to "come out of their comfort zones" and use creativity to address the problems faced by their patients in clinical trial participation. Some doctors want to support clinical trials but do not know how to access the resources that contain information about them. The Internet is one way to access information about clinical trials, but how many physicians have time to look up this information?

Another problem involves the small number of doctors in private practice who know about the phases of various clinical trials. Physicians must be educated on this topic before they send their patients to clinical trials. They also need to know what the trial offers patients in terms of advancing science versus offering a treatment or cure. Community-based physicians do not usually have patients who are interested in advancing science; their patients are interested in better medications or a vaccine. Both patients and clinical trials must be screened to determine their appropriateness given the needs and desires of each.

Educating the Patient

After a physician finds a patient who is compliant and would be a good candidate for an existing clinical trial, the physician must educate the patient about a clinical trial. At the same time, the referring physician must feel comfortable with the investigators and the trial protocol and must feel confident that his or her patient will be comfortable in the trial setting in terms of language and trust. In addition, the referring physician must explain to the patient why he or she is being sent to a different location for medical care.

Patients' expectations also play into the problem. If the patient is expecting treatment for a medical problem (e.g., an HIV patient who wants to try a new medication) and the trial is in the first or second phase, then treatment will not be available. Instead, participants will be screened for acceptance into a later phase of the trial. The issues of advancing science and financial gain also must be considered.

Uninsured Patients

An article titled "Enrolling the Uninsured in Clinical Trials: An Ethical Perspective" in *Critical Care Medicin*e[6] addressed some issues from the patient perspective that Dr. Hogan thought should be answered first by the referring doctor. The question involves the patient's lack of options. Regarding clinical trials, uninsured or underinsured patients have no other avenue to get treatment and are in a desperation situation. The doctor must consider which hospitals will take an uninsured patient and how long the hospital will accept Medicaid. Discovering a clinical trial puts pressure on the doctor and on the patient who has nowhere else to go and no access to medical care. If the trial involves medication, at the end of the trial the patient will be given a 3-month supply, but after that the patient reverts to Medicare, which does not have medication coverage. For example, a patient with non-Hodgkin's lymphoma might get treatment for the disease in a clinical trial, but when the trial is over, the medications cost $350 a month. The physician must question what his or her patient is going to do after the trial is over. A lack of health care options makes individuals susceptible to pressure to enroll in clinical trials. Where else can they go for state-of-the-art care? And where do they go after the trial for followup care and medication?

Dr. Hogan ended his presentation by stating a question likely to be asked by patients: "Why am I in such demand as a research subject when nobody wants me as a patient?" Likewise, he asked: "Why are you [investigators] all coming to my office begging for my patients?" What about the ethical issues involved in physicians using patients as bargaining chips for personal gain? The most significant ethical dilemma involves private physicians' lack of trust, which must be dealt with through education. In conclusion, Dr. Hogan stated that the number one reason that his patients continued their participation in the NIAID clinical trial was the positive treatment they received from the staff.

Discussion

Dr. Hogan's presentation prompted the following questions and comments:

- A participant voiced "the dirty little secret" that community and academic physicians do not refer patients to clinical trials because of politics and the fear of losing patients. One hospital does not want to lose patients to another, and oftentimes patients seek out clinical trials because they are not happy with the care they are getting from their private-practice physicians. Dr. Hogan agreed that physicians might fear losing patients through referrals. However, he pointed out that to be admitted into

[6] Pace C et al. Enrolling the uninsured in clinical trials: an ethical perspective. Crit Care Med 2003;31:S121-5.

a clinical trial, a patient must have a private doctor to whom the trial site can send the patient for care unrelated to the trial. Investigators must educate physicians about the requirement for trial participants to have a primary care doctor. Dr. Hogan also pointed out that providers must enlist the aid of their nurse case managers to keep a list of particular clinical trials and patients who might be qualified to enter them. Dr. Cargill mentioned a 2002 pilot survey of African American physicians on the topic of referral to clinical trials; the survey results confirmed the political nature of the problem.

- An attendee asked if financial incentives can be offered to primary care physicians for referrals to clinical trials, especially since many clinical trial participants see their primary care doctor very infrequently. Dr. Hogan reiterated that when patients are referred to a clinical trial, they must continue to see their primary care providers for comorbid conditions, such as high blood pressure and diabetes, because the trial investigators will not treat them for those conditions. The relationship between primary care physicians and patients must be maintained. Dr. Cargill added that a way to break down the barrier of mistrust regarding clinical trials is to emphasize the benefit that accrues when clinical trial information, such as lab values, is conveyed to primary care providers who then become involved in their patients' general health care. Although monetary rewards would not be appropriate per se, primary care providers could benefit from feedback about their patients. Dr. Hogan stated that a clinical trial that failed to convey lab results to a primary care physician does not deserve its referrals. Dr. Cargill added that a focus group of primary care physicians in Cleveland stated that one of the main reasons they would continue to refer patients to clinical trials would be to continue to get lab results, and one of the biggest reasons they would stop is because they failed to get the information about their patients. In addition, people who participate in clinical trials have a survival benefit. Another attendee pointed out that some clinical studies are not designed to deliver feedback. For example, phase I clinical trials are of no particular benefit to the patient; they are carried out to determine inclusion or exclusion.

RECRUITMENT AND RETENTION: WHAT WORKS AND WHY

Kathleen B. Drennan, Chief, Global Marketing and Strategic Business Development, Iris Global Clinical Trials Solutions, Chicago, Illinois

Ms. Kathleen B. Drennan remarked that in both the private sector and the Government, patient recruitment and randomization are major problems that impede successful clinical trials leading to new treatments. In addition to finding, engaging, and retaining patients, site variability and inefficient management are problems in the recruitment landscape. Today, a 6-month delay in enrollment for most clinical trials is common, and rescue studies have become prevalent because of problems with patient recruitment. An estimated $1 billion is spent today worldwide on patient recruitment.

Roadblocks exist in the recruitment landscape. Less than 10 percent of the eligible population participates in clinical trials. About 74 percent of people are unaware of clinical trials in this country. More than 26 percent of volunteers drop out of phase I and

phase II studies after giving informed consent. In addition, there is increased competition for patients in clinical studies. Only 3 to 4 percent of board-certified minority physicians worldwide participate in clinical trials. The figure in the United States is 3.7 percent, the same as it was 75 years ago. Furthermore, Ms. Drennan mentioned a diabetes trial in which 80 percent of respondents were white males.

Optimizing Recruitment and Retention

Ms. Drennan pointed out that when she became involved in cardiovascular research in 1975, at a time when medical practices were very large and before the widespread existence of HMOs, the sites were allocated money to find patients. The majority of sponsors of clinical trials today still approach clinical trials in a "local random" fashion. Multicenter trials are spread out over as many as 500 sites, and each site attempts to enroll patients on its own. Enrollment carried out in a nonintegrated, random fashion is undependable. A more centralized approach to recruitment, enrollment, and retention means doing upfront market research, targeting the messages to the right people in the right communities, and conducting focus groups to ascertain whether a protocol will work with a real population. If managed properly, shared media can work in the right protocols and in the right situations, as can centralized call center services, which can help volunteers, patients, and sites.

Optimizing the process of patient recruitment will result in the ability to predict return on investment (ROI) in a clinical trial. ROI entails more than just money; it entails investment in time resources and investment for those people who need new therapies and treatments. The recruitment process is extremely important to offset "the leaky pipe" whereby patients are lost to clinical trials.

If less than 10 percent of eligible potential volunteers in this country participate in clinical trials, a significant number of them are needed at the top of the funnel. Up to 75 percent of study volunteers drop out or are lost before they even get to the study site for screening. Frustration results for study sponsors who establish trial sites; spend money on media, programs, and community outreach; and recruit volunteers, but still cannot get randomization. To optimize retention, volunteers must be tracked from the very first point of contact.

Ms. Drennan cited a case study to demonstrate the "if you can't measure, you can't manage" maxim. A recent study done in rescue mode found that 50 percent of the patients dropped out at the prescreen stage, that is, at the very first time they called the site to determine whether they were eligible. Another 25 percent dropped out at the actual screen visit, and another 20 percent at randomization. Therefore, by the time of randomization, a large volume of patients is needed to populate the study.

The question concerns how to measure the leaky pipe along the way to ensure in the early stages that the study will be completed. Without sufficient volume at the beginning of the randomization stage, the study will not be completed. Patients are lost because they are not contacted. They might have inquired about a study, they might have seen an ad or

poster, or they might have heard a radio or television program. They call an 800 number and leave a message, but nobody gets back to them. If they are not contacted within 24 hours, they are lost. A majority of sites today lack the proper resources to respond quickly. The regulatory environment demands a great deal of clinical sites; however, resources have not been allocated to enable the sites to recruit patients into studies. Patients do not understand study requirements, and prescreeners can be very inexperienced and lack training. Increased patient volume depends not merely on numbers of patients but on numbers of qualified patients.

Metrics in Action

Managing a study depends on being able to measure recruitment data along the way. To optimize recruitment and retention programs, certain factors come into play:

- Call center referral management
- Site support and benchmarking
- Cost efficiencies
- Patient delivery

Ms. Drennan described a urinary incontinence case study with difficult enrollment. In rescue mode, the timeline for the study, without measurement, projected that the study would be completed at the end of 2005. By using measurement and centralized management, the study reached completion in August 2003. From that change, one can extrapolate the savings of time, money, and resources.

In this particular study, there was an increase of 25 percent in randomization and a decrease in time that equated to a 25-percent decrease in the cost of the trial. Accurate real-time measurements allow for projections and benchmarking, and up-to-date information enables quick strategic adjustments. On the other hand, the study can be put in jeopardy if it takes 3 or 4 weeks to discover that a strategy in place at the majority of sites is not working. In short, study metrics are the foundation for future successful projects in a particular therapeutic area.

Call Center Referral Management

By the time this particular study was in rescue mode in May 2002, only 82 patients had been randomized over an 11-month period. The proposed goal was 418 patients over the next 18 months. A call center, or patient interaction center, was established with IRB-approved scripts to prescreen callers for eligibility for the trial. Sites that allowed the call center to set up the initial appointment were more likely to enroll patients in a shorter period of time and enroll a higher percentage of patient referrals.

Allowing a central system to schedule appointments and sending materials to the patients to educate them about the trial resulted in about 46,000 patient contacts made to the call center and more than 13,000 prescreened patients sent to individual sites. Because many sites refused to use the centralized call center, MyPatient.com was initiated so that those

sites could use interactive visit scheduling and manipulate the schedules themselves. However, once the sites realized the efficiency involved in the centralized call center, about 80 percent of the sites allowed the first appointment to be scheduled.

Site Support and Benchmarking

In this particular study, a full-blown media campaign was used to enhance recruitment. The data drove the call center allocation across all of the sites. Early indicators of site performance showed that the percentage of referrals completing their initial appointment was a good measure of the site's ability to enroll patients referred from the call center. Site performance could be predicted by the percentage of patients referred who completed their initial appointment. Therefore, the metric is an excellent early indicator of overall site performance.

To predict a site's retention capabilities, several early indicators are available:

- Number of initialized patients who complete the first visit
- Percentage of eligible patients who complete the second visit
- Percentage of eligible patients who are randomized
- Percentage of initialized patients who are randomized

The percentage of initialized patients who were randomized per site indicated when the study might be completed. Instead of just hoping and waiting ("vacant hope"), the study investigators and sponsors could make a fairly accurate prediction about when the study would end.

In terms of site scheduling, sites with unusually long time periods between the referral date and the initial appointment date could be identified and offered assistance. One site took an average of 81.2 days to schedule its first appointment, another site took 59 days, another took 24 days, and so on. Without the metric indicating the need for further resources to help the sites keep up, dollars would be wasted on media spending. The appointments-pending report that resulted from this metric also showed which sites might be overloaded with referrals and might need help to prepare for higher patient volume.

Cost-Efficiencies

By examining media costs for each market, adjustments were made immediately to optimize the media dollars spent each week. In this trial, which used newspaper, radio, and direct mail, newspaper was a significantly higher cost compared with the other media. Aggressive management of media spending resulted in the reallocation of resources. The average cost per referral was reduced from $860 per referral for advertising alone in week 1, to $300 per patient referral in week 15 of this particular campaign. The data-driven adjustments translated into a savings of $681,000 over the first 15 weeks. In this small phase II trial, more than $2.3 million would have been spent on media; instead, $1.6 million was spent.

A phase II clinical trial of type 2 diabetes showed similar media cost-efficiency. Before resolving to spend millions on media for this very pivotal study, the sites and markets were tested. A small percentage of the funds allotted for recruitment for this study was used to do a small test phase in 16 sites. This study was rescued almost 2 years earlier than planned, thanks to the intercessions, which determined upfront costs and effectiveness. Noneffective tactics and strategies were eliminated, site performance and referral threshold were measured, and the referral volume was adjusted.

A metrics analysis regarding media cost-efficiency (1) tests and assesses various media channels to determine high referrals at low cost per referral, (2) uses a test phase to determine at a low upfront cost which media are effective and efficient to reach the target demographic, (3) eliminates ineffective media channels early on in the recruitment process, (4) measures site performance and referral threshold capacity, (5) estimates the referral volume by the sites' location and size to adjust funnel projections, and (6) tests various creative elements to proceed with the most effective message.

Patient Delivery

A metric system can identify potential problems in patient delivery. Any unexpected drop in call volume, drop in qualified referrals, drop in randomizations, or increase in dropouts can be measured in real time and recognized quickly through online reports that are updated daily. In the urinary incontinence study, the results were that the study was finished early. A 45-percent increase in randomization occurred because of very simple, user-friendly, Web-based e-mail—not large expenditures in technology. Very simple measures were used to communicate and to connect all the parties involved in the trial.

Ms. Drennan ended her presentation by listing the advantages of using performance-based metrics management. Integrated, metrics-based, centralized recruitment will

- Shorten the enrollment timeline or accelerate the randomization rate
- Optimize the media dollars spent
- Empower the study team with knowledge about costs, time, and spending
- Ensure that every volunteer is tracked
- Provide a deep database of patient and recruitment information that can be leveraged for future studies
- Give the study team decisionmaking tools for a new project, enlighten management, and instill confidence in the strategic direction

Performance-based metrics management does not lose sight of the human dimension. It instills real-time measurements, whether in a large NIH study or an industry-funded study, and brings real solutions to the problems of recruitment in clinical trials.

Discussion

Ms. Drennan's presentation prompted the following remark:

- A participant reported on her recent attempt to be admitted to a clinical trial. After 3 or 4 weeks of phone calls and e-mails with the patient coordinator to schedule a screening visit, the individual discovered that she was not qualified to enter the trial. A more efficient prescreening process or a Web site with detailed protocol and informed consent information would have prevented the significant waste of time and resources experienced by this individual. Her experience demonstrates that sites should invest money up front to prevent this type of inefficiency. Ms. Drennan pointed out that the example shows how a study can be accelerated by conducting upfront screening in a centralized way. In addition, in a coordinated prescreening effort, the prescreening center can send out "patient kits" or "site kits" with information about the trial, or the center can refer the volunteer to the Web for the material. In addition, a consent form can be accessed from a CD-ROM, or a video can explain information about the trial and possibly screen out ineligible individuals early on.

REACHING ADOLESCENTS IN CLINICAL RESEARCH

Donald P. Orr, M.D., Professor of Pediatrics, Nursing Research, and Dietetics and Nutrition, Director of Adolescent Medicine, Indiana University School of Medicine, Indianapolis, Indiana

Dr. Donald Orr began his presentation by describing the issues that investigators face when they target adolescents as research subjects. Adolescents are at the highest risk for sexually transmitted infections (STIs); therefore, they often are the target population for research. They are difficult to deal with because both society and their parents do not want to contend with sexually active adolescents. Dr. Orr reported on recruitment and retention in the Indianapolis Young Women's Project.

Adolescents as Research Subjects

As research subjects, children are a special population. Under NIH guidelines, children are considered a vulnerable population needing additional protection, according to the Code of Federal Regulations (CFR). Special guidelines for research involving children call for defining minimal risk in the context of the lives of children instead of in the context of the population. If the research does not benefit them, doing greater than minimal risk research is very difficult. One must define the benefits of participating in the research.

The informed consent process presents specific, special issues for vulnerable populations. Does a 16-year-old, sexually active adolescent have the capacity to consent? Does an adolescent who is not sexually active have the capacity to consent? Who can consent when enrolled in a clinical trial? Is it the parent? What if the research involves a sensitive topic and the adolescent—the minor—does not want his or her parents to know he or she

is sexually active, but divulging the participation in a clinical trial would reveal that? How does one obtain parental permission when the research involves a sensitive topic? Can active consent or permission or passive consent or permission be used? Should a guardian ad litem be assigned to enroll minors in projects?

Using adolescents as research subjects also raises questions about protection, compensation for participation, and access to subjects:

- *Protection.* Adolescents must be protected from harm, but what level of harm is justifiable? Adolescents' confidentiality also must be protected, but to what extent? In addition, adolescents deserve "distributive justice," or fairness, but what about targeting specific populations and offering equal access to potential benefits in research?
- *Compensation for participation.* What is fair compensation for participation? The amount should be noncoercive, but how is that defined for a minor? What form should the compensation take? Money? Vouchers? Prizes? Raffle tickets? Who should be the recipient of the compensation? The adolescent? The parent?
- *Access to subjects.* How can researchers gain access to a population of minors?

Mid-America Adolescent Cooperative STD Research Center

Dr. Orr described the Mid-America Adolescent Cooperative STD Research Center, which is engaged in research on adolescent STIs. Based at Indiana University with co-operations at the University of Iowa, Northwestern University, and Louisiana State University, it is one of the seven NIAID-funded cooperative research centers on STIs and the only one devoted entirely to adolescents.

Indianapolis is a medium-sized Midwest city with a population of approximately 750,000. About 20 percent of the population within greater Indianapolis is African American, and less than 5 percent is Latino. There are essentially no other minority populations within the greater Indianapolis area. Because this community is very conservative, doing research about sexuality is very difficult. In fact, many legislators in the area have attempted to close down many of the projects. The researchers work within primary care adolescent clinics that are part of the urban health system. About 60 to 70 percent of the patients are African Americans.

Young Women's Project

This longitudinal study attempts to look at behavioral, psychosocial, and biological risk and protective factors for lower-tract STIs in 300 14- to 17-year-old women from 3 adjacent adolescent clinics. Adolescents are enrolled in the study without regard to sexual experience or infection status. This facet of the study design creates problems for parents who are concerned that in some way the researchers are deceiving them. Because it is a study of STIs and risk factors, parents perceive that their daughters are considered

sexually active or that being in the project will encourage them to become sexually active. This perception is one of the major difficulties in recruitment.

Dr. Orr stated that the Young Women's Project is a very intrusive study. It collects quarterly clinical and biological specimens involving pelvic examinations in addition to very personal behavioral data. For 6 months of the year, the researchers collect daily diaries and weekly biologic samples (self-obtained vaginal swabs). Some cervical biopsies are collected on a very limited basis with the older patients. The study includes a questionnaire, interviews, a whole host of specimens, and a parent questionnaire at enrollment, at 12 months, at 24 months, and beyond.

Issues Involved in the Young Women's Project

Dr. Orr described the issues involved in the project:

- The researchers needed to obtain both parental permission and adolescent consent.
- The researchers acknowledged the sensitive nature of the topic with the parents and subjects and called for shared trust involving the parent, the adolescent, the clinics, the community, and the researchers. The researchers also announced their resolve to protect the participants' confidentiality. In addition, the researchers knew they might have to handle the potentially negative impact of the study being discussed or misrepresented in the media.
- There was a large subject burden. The study was demanding, intrusive, and invasive in many ways, both personally and physically.
- The longitudinal study is in its fifth year, with hopes of being extended for another 5 years. The study has collected over 30,000 days of diary entries and other forms over the 5 years of study.

Progress, Retention, and Data Collection

The project has enrolled 220 adolescents, the majority of whom (192) are African American. That number basically represents the composition of the clinics. A total of 25 of the enrolled adolescents are white, and 3 are Hispanic. Twenty-one adolescents dropped out of the study because of the time involved or because they moved or were no longer interested. Most of them withdrew within the first 3 months of the study. The retention is approximately 85 percent at 3 years, which is quite good considering it is a difficult population.

Dr. Orr stated that the study collects diary data for 84 days every 6 months. The diaries tell about social and sexual contacts, sexual behaviors, substance use, mood, and symptoms. The subjects also provide weekly vaginal swabs, which are analyzed for a multitude of infectious agents. The swabs are collected at the homes by field assistants.

Steps Involved in Conducting the Study

Dr. Orr described the steps that the researchers took to engage the community, including the clinics in which they were working. The clinics are a major player in the health care of the youth in Indianapolis.

- The researchers met with the community leaders and organizations, including the head of the public health department, parents who were identified by the community and various other individuals as being important key players, the health center advisory boards, youth-serving organizations, and the police department. The study addressed the important problem of adolescent sexuality and STIs. The areas under study have the highest prevalence of STIs in the country; in fact, a square mile area north of the study area was identified as having the highest rate of syphilis in the United States. When that fact reached the media, it helped raise the level of awareness within the community regarding the importance of the topic.
- The researchers attempt to be honest and up front about the objectives of the study and to show how the study is built on experience with earlier studies. They conduct exit interviews and have discussions with the adolescents and their parents about their participation in the study. The study also provides regular feedback to the clinics and the advisory boards.
- The research staff joined the clinical staff to create a team. Everyone who works in the three clinics is regarded as part of the team. As providers, the researchers are all very visible in the community and the clinics. The clinics are reimbursed for the use of their rooms.
- The team is well trained and supervised. The researchers attempt to identify people who are caring and sincere. The team is made up of an ethnically diverse population. Weekly team meetings are run by a project manager who has a high school education—not by the PIs. The researchers attempt to make adjustments based on the feedback from the team and the clinics. They give positive feedback to the clinics and to the team itself.
- The researchers enroll parents and adolescents and obtain written informed consent and permission from both. The researchers are up front about the study purpose and explicit about confidentiality. They announced that they would give confidential information about the adolescent to the parent if it happened that the child had an STI or became sexually active. Researchers explained that if they found anything that they believed was dangerous about a child or something that might jeopardize a child in any way, they would talk with the adolescent and then inform the parents.
- The researchers reimburse the participants at the level of unskilled workers. The participants also get free treatment and intensive screening for infections. The incidence rates within 3 months showed that 30 percent of the young women had a second sexually transmitted infection.
- The researchers maintained frequent contact with the adolescents. They were seen weekly during intensive data collection. The subjects made quarterly clinic visits, and contact information was updated regularly. The subjects do not move a great deal, but

their phone numbers change frequently, so the researchers attempt to have multiple contact points and send the subjects reminders for visits. They also send the participants birthday cards and holiday cards.

Subjects' Willingness To Participate in the Study

Dr. Orr discussed the study's use of exit interviews, which asked salient questions about the reasons for participating in the study; they also asked the parents similar questions. Their candid responses included (1) the researchers' honesty with parents and adolescents about the study, (2) the researchers' ability to inspire trust, that is, to know what to say and how much to probe without appearing too intrusive, (3) the caring quality of the staff, including their respect, openness, and willingness to accept the adolescents' beliefs, attitudes, and behaviors without being judgmental, (4) the adolescents' ability to be themselves and use their own language, (5) the staff's encouraging the adolescents to achieve their personal goals, (6) the staff's willingness to listen to the subjects and to communicate with them as friends, and (7) the team's ability to establish a rapport with the subjects and the parents.

In addition, the young people liked the reminders they received by telephone or by mail as an incentive to keep their appointments. As a couple of the young women said, "This is a talented team who cares about what adolescents do." They did not mention the money, although it clearly helped them.

Dr. Orr concluded his presentation by offering the following suggestions about recruitment for clinical studies:

- Ensure that the project has scientific importance.
- Know the community.
- Ensure that the study is relevant to the community by accurately assessing the community's needs.
- Engage the community.
- Build a skilled research staff.
- Develop a rapport with the participants.
- Provide ongoing feedback.

Discussion

Dr. Orr's presentation prompted the following questions:

- A participant who is an applied anthropologist and an ethnomarketer asked whether the researchers had to deal with aspects of extended family because of the fictive kin aspect of family integration and cohesion in the African American community either in terms of recruitment or ability to assent. Dr. Orr responded that the researchers

viewed the family as whoever came and spoke to them. To participate, a young woman had to first indicate she was interested, and then her guardian, usually her mother, had to agree to allow her to be in the study. Next, the researchers asked the mothers if they would participate in a parent capacity.

- Another participant asked whether in the hypersegregated communities of the clinics, the data reflected same partners. Dr. Orr responded that same partners were found anecdotally in the study through the diaries.
- An attendee asked Dr. Orr to elaborate on the interview. Dr. Orr explained that the enrollment interview was a semistructured interview after consent combined with one-page daily diary entries. The diaries were collected each week. Then 3 months later, a structured interview was conducted to ascertain behavioral collection data in the interval. With trained interviewers or research personnel, adolescents can be easily engaged in this type of interview.
- Another attendee asked about the resources in terms of effort, time, and planning and the knowledge needed to generate a budget for a proposal that adequately reflects what it costs to do what has been described. Dr. Orr replied that the budget must estimate recruitment, reimbursement, and staff salaries. An attendee mentioned that the biggest cost-eaters in a budget involve tracking time.

CONCURRENT SESSION REPORTS

The discussion leaders of the concurrent breakout sessions reported on their discussions.

Session I: After the Clinical Trial—Then What?

Dr. Limacher listed four themes that emerged from the breakout session:

1. Be prepared for the end at the beginning. Plan for two scenarios—a timely, planned closeout and an untimely, early closeout. Likewise, the clinical trial personnel should facilitate transitions from the research setting, particularly if the research participant depends on the clinic setting for other forms of clinical care, so that he or she can transition back to the provider or on to a new clinical provider early in the study. That planning should be part of both the proposal and the protocol.
2. Involve participants in planning for the closeout, communicate how and when the study results will be revealed to them, and follow through with the plan. The involved providers should be updated regularly about the activities of the trial and should be informed about the outcome of the study. Community partners should be fully involved as well. Likewise, individuals who are screened out at the beginning should be involved in networking for future studies.
3. Distinguish research from clinical care while recognizing that overlap exists, particularly when the research study is the only current care provider. Researchers must consider the possibility that care is an incentive for participation. Other care provisions should be planned from the beginning of the study.

4. Require participants to have a primary care provider. The research community should support efforts that will ensure health care for all Americans.

Session II: Minority Investigators in Clinical Trials—How Important Are They?

Dr. Evans reported on several themes that emerged from the breakout session:

1. Acknowledge the need to increase the number of minority investigators and the difficulty in recruiting these individuals. Minority investigators are critical for successful recruitment of diverse participants, especially for training nonminority researchers in appropriate methods to increase diversity in clinical trial studies. The relationship between minority and nonminority researchers must be transformed.
2. Design studies statistically powered to answer gender and racial/ethnic research questions.
3. Recognize the role of minority and community-based health care providers as important partners and co-investigators.
4. Encourage nonminority investigators to find ways to improve participation rates among diverse segments of the population through (1) training more minority nurses and nurse practitioners as well as study staff who are culturally proficient, (2) volunteering at medical service clinics in relevant communities, (3) building a research infrastructure that is both ethnically diverse and diverse in terms of professional training, and (4) seeking mentors who are successful minority investigators or successful in recruiting diverse cohorts to trials.
5. Support the idea that partnerships between community institutions and universities can help accomplish recruitment goals.
6. Establish the long-term benefit for participants in terms of drugs, access to care, and health information.
7. Recognize the significant disparity in research resources in rural versus urban areas.
8. Recognize the ability of minority investigators to incorporate humanistic and spiritual values in the research infrastructure and in health care.
9. Develop appropriate incentives for nonminority investigators to include minority participants in trials.
10. Design research studies with specific goals and benefits that appeal to diverse cohorts.
11. Uphold cultural proficiency as an important factor in clinical research.
12. Ask if there is a role for partnership of NIH clinical trials infrastructure and AHRQ to provide program enhancements for research aimed at increasing participation rates.
13. Continue to challenge the validity of data not obtained from a diverse population cohort.

Session III: Role of the Community Advisory Board and Outreach Activities

Mr. Murguia explained that the breakout session involved a discussion of the role that community advisory boards play from both a community and a principal investigator perspective. The session included the following topics:

1. The advisory function of the community advisory board
2. What community advisory boards can and cannot do
3. The components of a successful community advisory board
4. Ensuring parity, inclusion, and representation on a community advisory board
5. The location and timing of meetings, creating a sense of ownership on the part of board members for the work they do in the community, ensuring dialogue within the community and between the site and the community advisory board, and strong principal investigator involvement

Ms. Madey reviewed the breakout session's emphasis on the importance of defining community from the point of view of the goal and purpose of the research.

CLOSING REMARKS

Dr. Hernandez thanked the participants and reminded them that the symposium proceedings would be posted on the Web. In a summary of the topics discussed at the symposium, Dr. Hernandez mentioned cultural issues, system issues, logistics, what happens after the clinical trial ends, the role of the minority investigator and the trial coordinators, and referring physicians. He ended by drawing attention to the need to populate a future symposium on health disparities with people who are not "in the choir."